The majority of the population prefer the certainty of irrational conviction — to the uncertainty of logical doubt

J. Thomas Payte, MD

Opioid Maintenance Therapy (OMT);

- *The Science & Pharmacology*
- *How it works*
- *Impact of OMT*
- *Induction, maintenance & withdrawal*
- *Holders, Non-holders, & Serum Levels*
- *Pregnancy*
- *Pain*

Early Efficacy & Outcome Studies

- Retention - VS. TC and Drug Free
  - –NYC, DARP, & TOPS (>40K patients)
- Retention relative to dose/placebo
  - –Newman, Strain, & Caplehorn
- Reincarceration and heroin use
  - –Dole, Newman & Whitehill (‘69 & ‘76)

Efficacy: Retention Studies
Modality Comparisons

Study	Size	Modality	Dropout %/wk
DARP	12,294	MMT	1.4
		TC	3.2
		Drug Free	4.7
TOPS	9,989	MMT	2.0
		Residential	3.7
		Outpatient	4.8

Opioid Agonist Treatment of Addiction - Payte - 1998

Efficacy: Retention Studies
Methadone Modality

Study	Size	Treatment	Dropout %/wk
NYC	20,603	MMT	0.76
Newman	100	MMT	0.85
		Placebo	7.1

Efficacy: Retention Studies

Methadone Modality by Dose

Study	Size	Treatment	Dropout %/wk
Strain	212	50 mg/d	2.3
		20 mg/d	3.6
		Placebo	7.1
Caplehorn	238	>80 mg/d	0.3
		60-80 mg/d	0.8
		<60 mg/d	2.1

One year outcome randomized controlled trial
Dole et al., 1969

	Reincarcerated?		Daily Heroin Use?	
	Yes	No	Yes	No
Methadone	6	10	4	12
Control	16	0	16	0
Odds Ratio*	53.31		91.67	
95% confidence interval	2.71 to 1048.2		4.51 to 1864.92	

*Odds of control VS methadone

From Key Issues in MMT - Ward, Mattick, and Hall - 1992

Randomised controlled trial at three-year follow-up

Newman and Whitehill, 1976

	Retained in Treatment?		Discharged for Heroin Use?	
	Yes	No	Yes	No
Methadone	28	22	8	14
Control	1	49	31	18
Odds Ratio	62.36		0.33	
95% confidence interval	7.97 to 487.90		0.12 to 0.94	

From Key Issues in MMT - Ward, Mattick, and Hall - 1992

Pharmacology - Methadone

- Almost pure mu agonist
- Oral - 80-90% oral bioavailability
- Extended duration of action in suppressing opioid withdrawal (T-1/2 = 24-36 hours)
- Single dose analgesic properties similar to morphine in potency and duration
- Accumulation with repeated use for pain can result in sedation and respiratory depression in the non-tolerant patient

Source: Goodman & Gilman

Absorption - Methadone

- Detected at 30 min. following oral dosing
- Peak plasma levels occur at 2-4 hours
- Large amounts stored in liver and other tissues for later release into circulation to maintain steady-state (Reservoir Effect)
- Protein binding extensive, up to 90% of therapeutic dose
- Highly lipophillic, parenteral doses readily cross blood-brain barrier

Source: Goodman & Gilman, Kreek, and others

Metabolism/Excretion - Methadone

- Extensive bio-transformation in liver
- N-demethylation and cyclization to form principal metabolites:
  - pyrrolodines (EDDP)
  - pyrroline (EMDP)
- Metabolites are essentially inactive
- Metabolites and unchanged methadone are excreted in bile and urine

Source Goodman & Gilman, Kreek, Baselt, and others

Urinary pH Disposition of Methadone

Urinary pH	5.2	7.8
Methadone Plasma Half-life	19.5 +/- 3.6 hours	42.1 +/- 8.8 hours

Source: Nilsson et al., 1982

THE BASICS:

HOW IT WORKS

GOALS FOR PHARMACOTHERAPY

- Prevention or reduction of withdrawal symptoms
- Prevention or reduction of drug craving
- Prevention of relapse to use of addictive drug
- Restoration to or toward normalcy of any physiological function disrupted by drug abuse

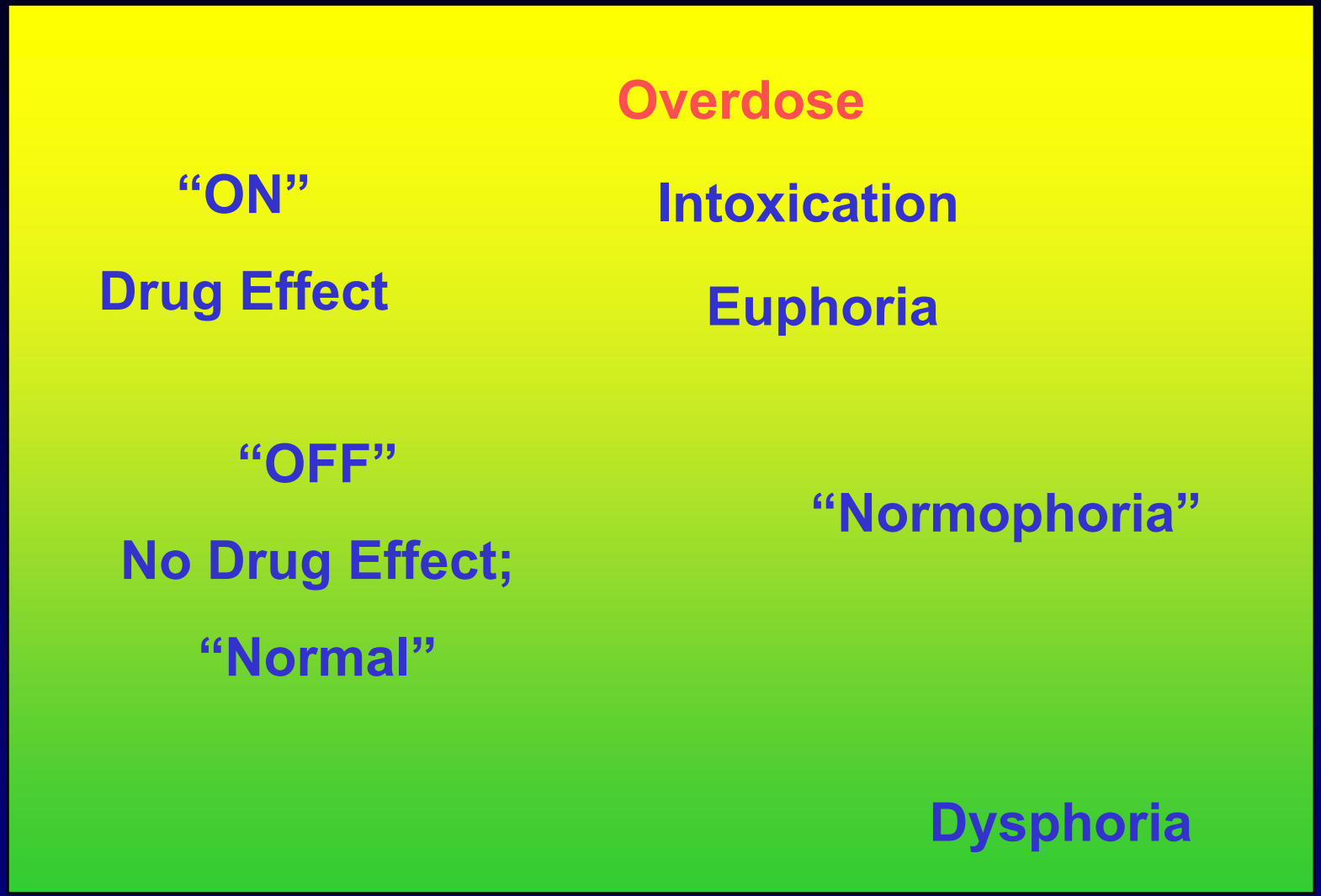
Source: MJ Kreek, Rationale for Maintenance Pharmacotherapy of Opiate Dependence, 1992

PROFILE FOR POTENTIAL PSYCHOTHERAPEUTIC AGENT

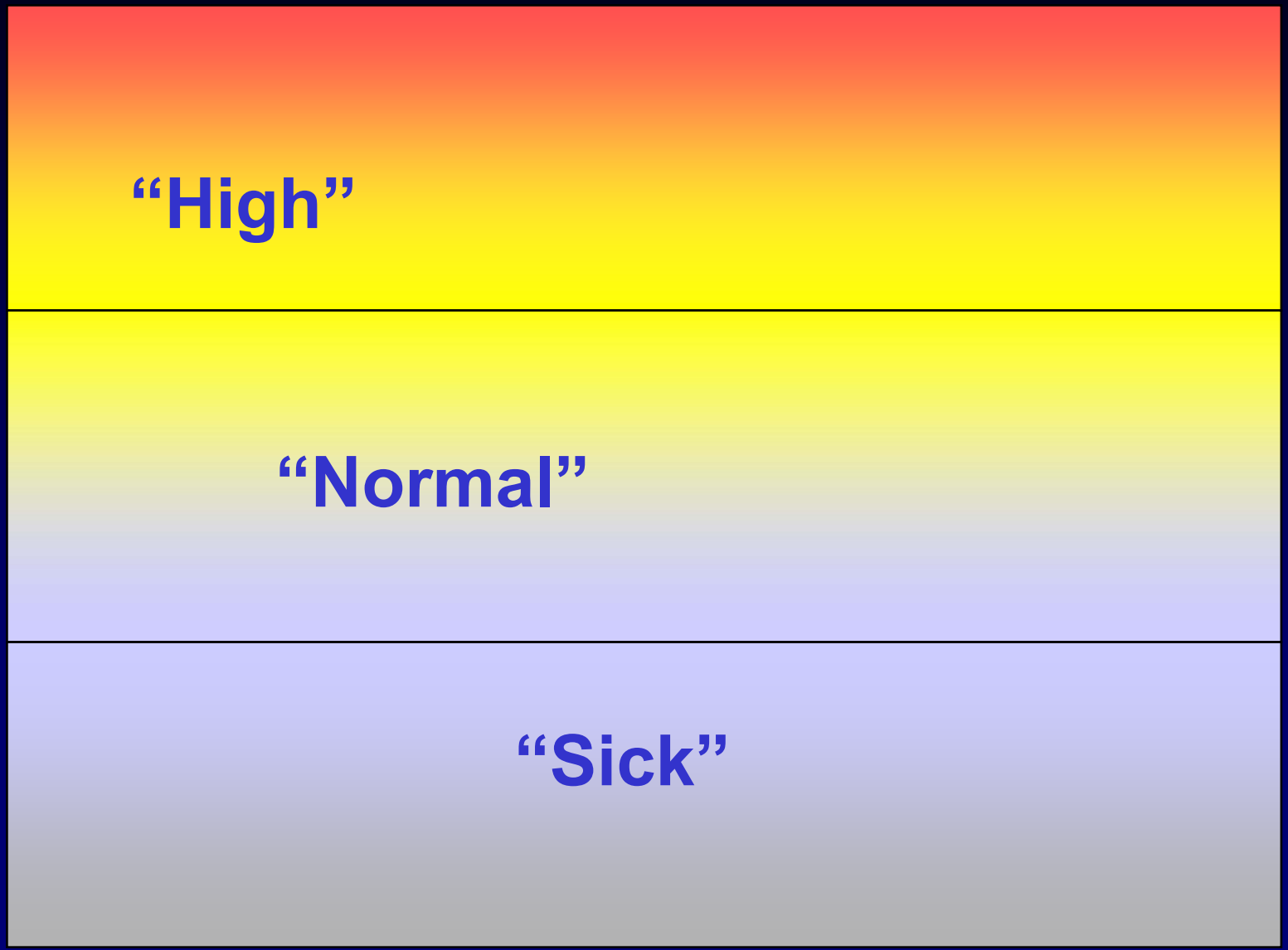
- Effective after oral administration
- Long biological half-life (>24 hours)
- Minimal side effects during chronic administration
- Safe, no true toxic or serious adverse effects
- Efficacious for a substantial % of persons with the disorder

Source: MJ Kreek, Rationale for Maintenance Pharmacotherapy of Opiate Dependence, 1992

On/Off - Non-Tolerant Drug States



Tolerant / Dependent States



Development of Tolerance/Dependence
…loss of on/off condition

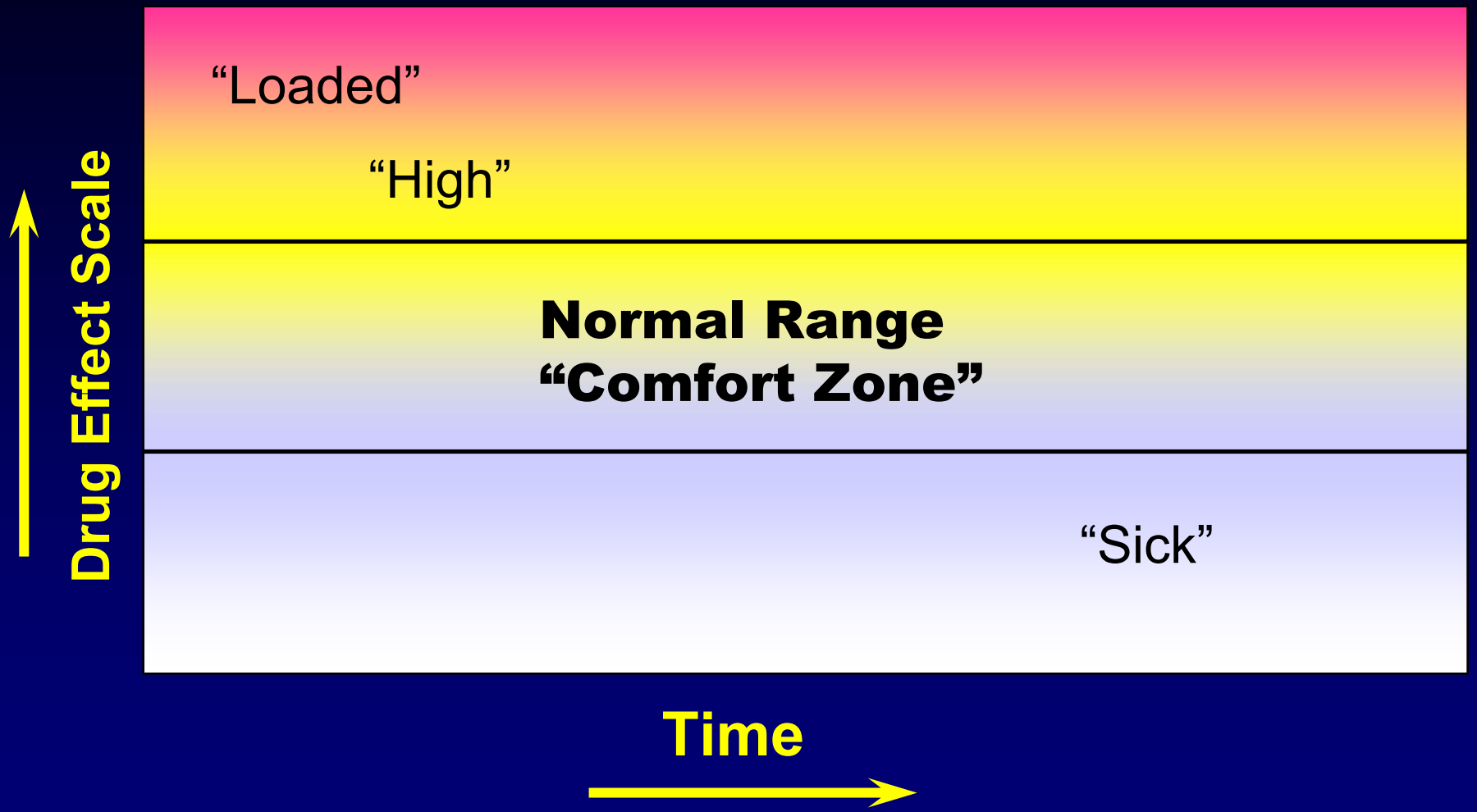
— with continued and repeated use

Tolerance develops (↑ dose for desired effect)

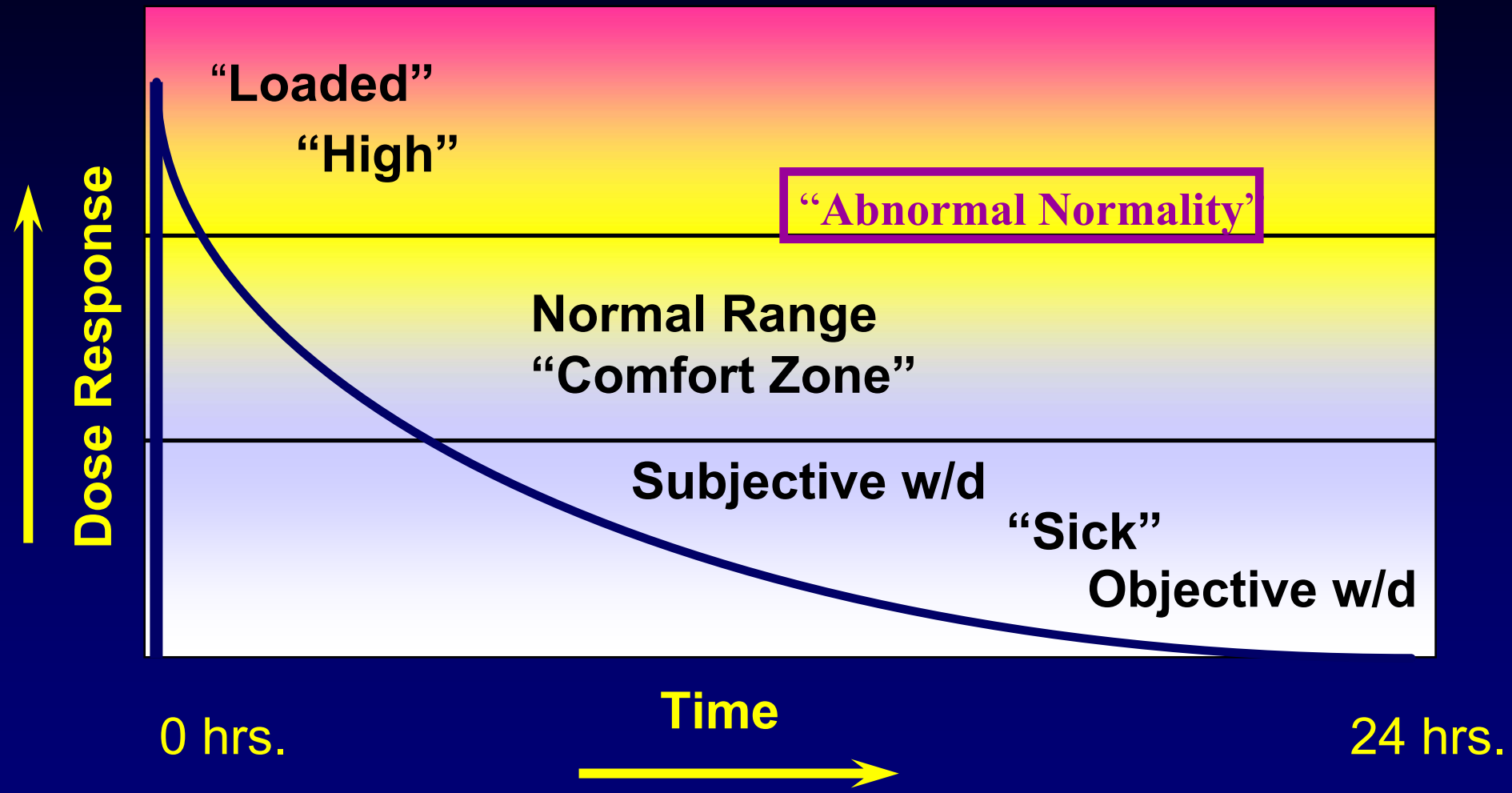
Physical dependence develops (Withdrawal syndrome on abrupt cessation of the drug)

Leading to:

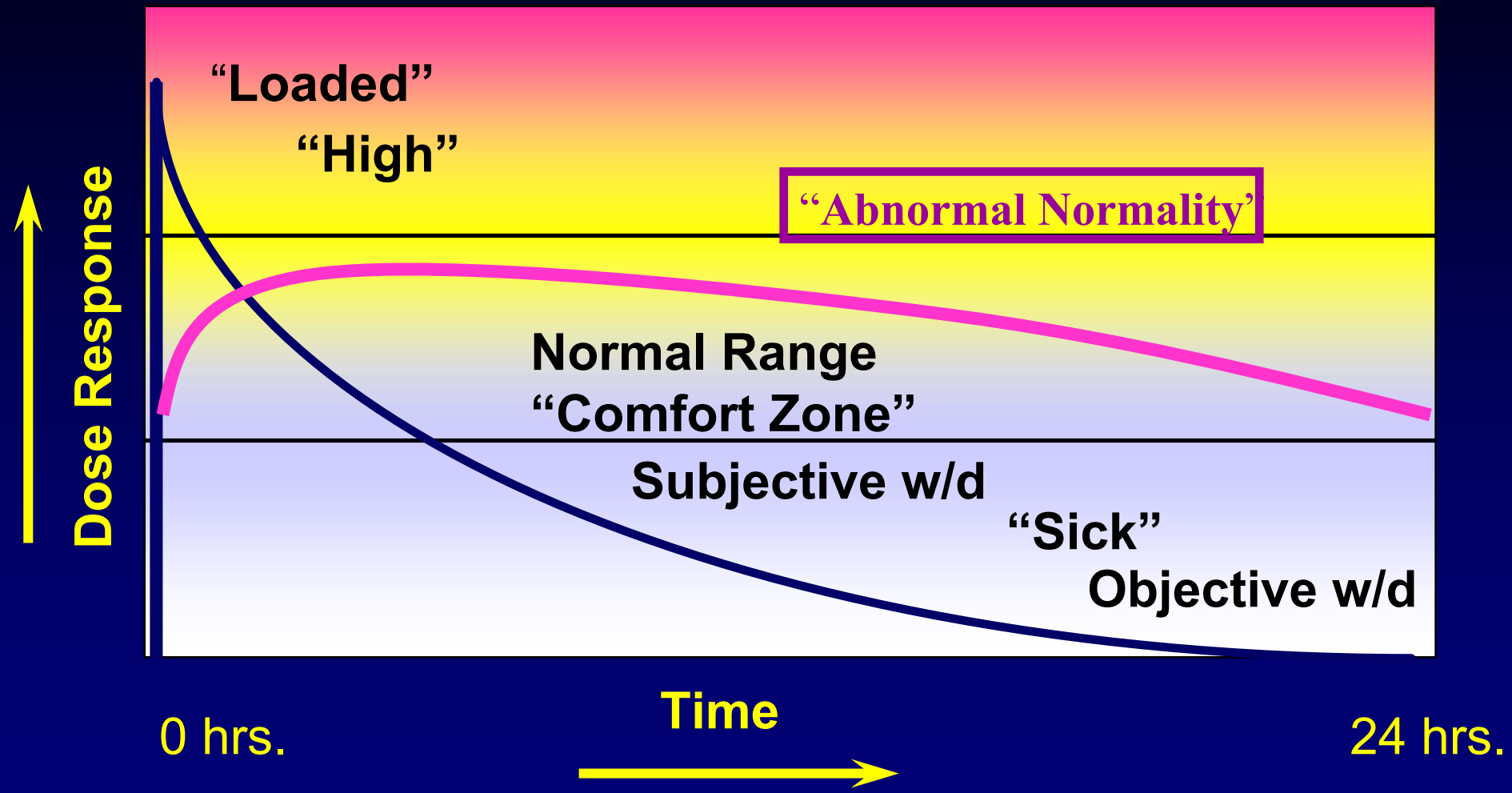
Tolerant/Dependent Drug States



Heroin Simulated 24 Hr. Dose/Response
With established heroin tolerance/dependence



Methadone Simulated 24 Hr. Dose/Response
At steady-state in tolerant patient



What Does OMT DO?

Impact of Treatment!

Impact of Maintenance Treatment

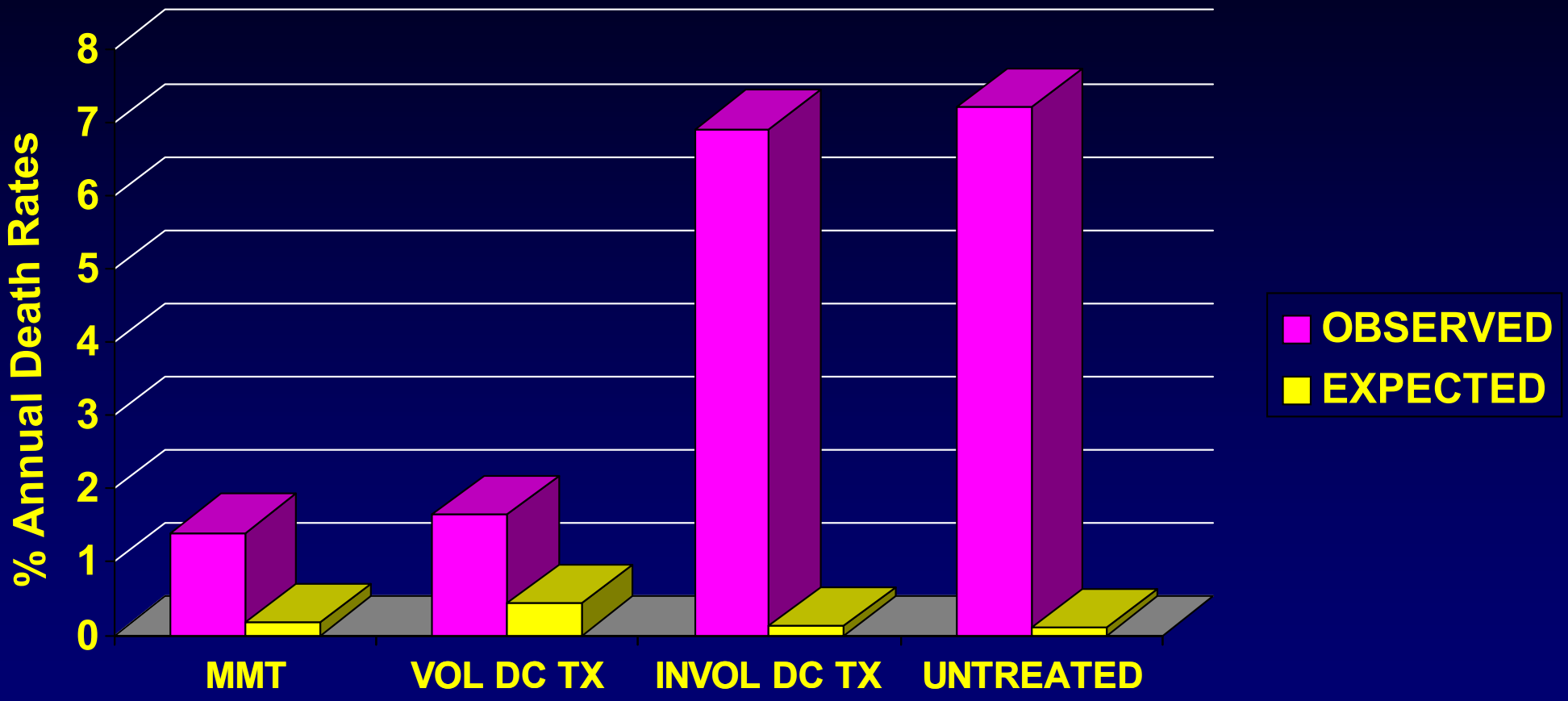
- Reduction death rates (Grondblah, ‘90)
- Reduction IVDU (Ball & Ross, ‘91)
- Reduction crime days (Ball & Ross)
- Reduction rate of HIV seroconversion (Bourne, ‘88; Novick ‘90,; Metzger ‘93)
- Reduction relapse to IVDU (Ball & Ross)
- Improved employment, health, & social function

DEATH RATES IN TREATED AND UNTREATED HEROIN ADDICTS

	MMT	VOL DC TX	INVOL DC TX	UNTREATED
OBSERVED	1.4	1.65	6.91	7.2
EXPECTED	0.17	0.44	0.13	0.11
OBSERVED/ EXPECTED	8.4	3.8	55.3	63.1

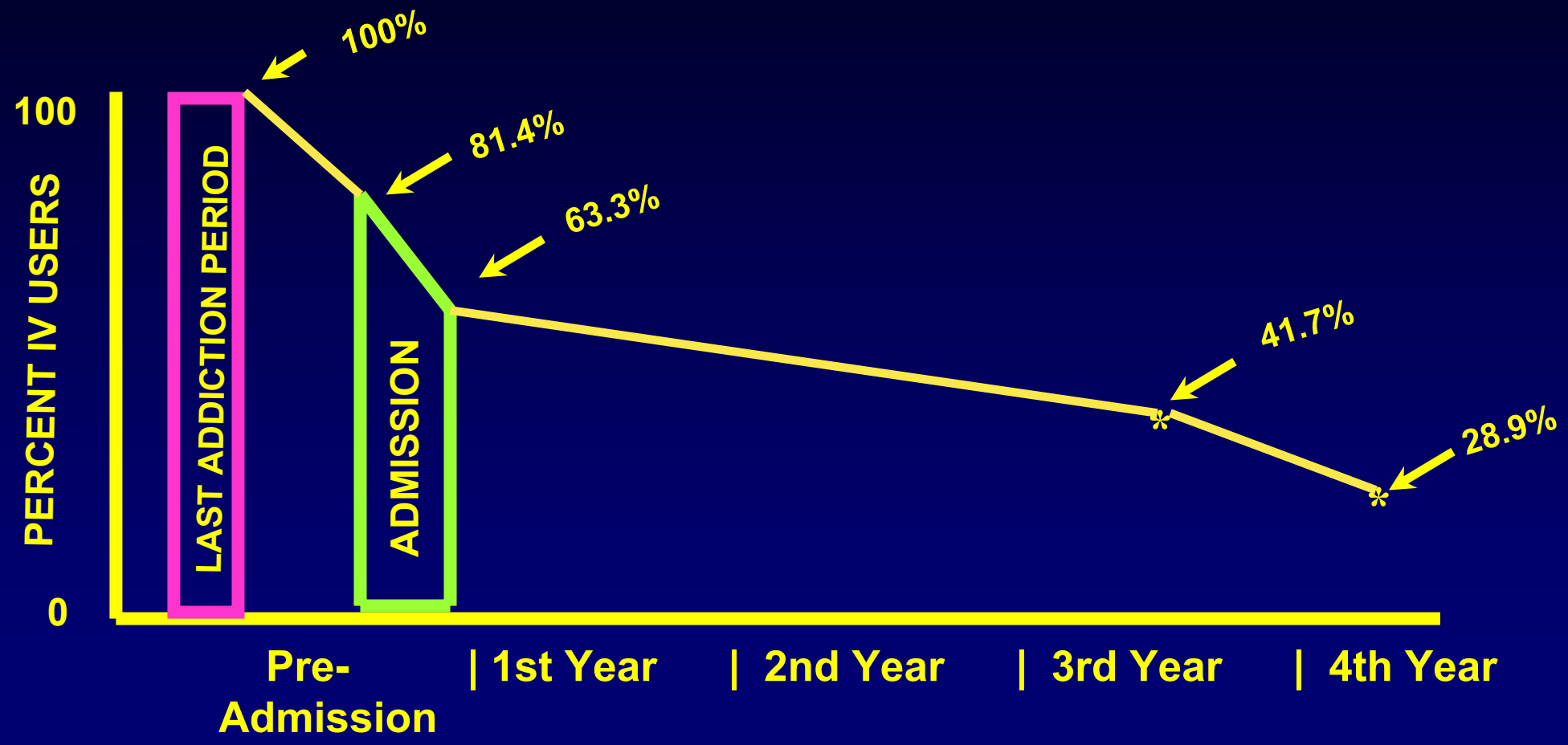
Slide data courtesy of Frank Vocci, MD, NIDA - Reference: Grondblah, L. et al. ACTA PSCHIATR SCAND, P. 223-227, 1990

DEATH RATES IN TREATED AND UNTREATED HEROIN ADDICTS



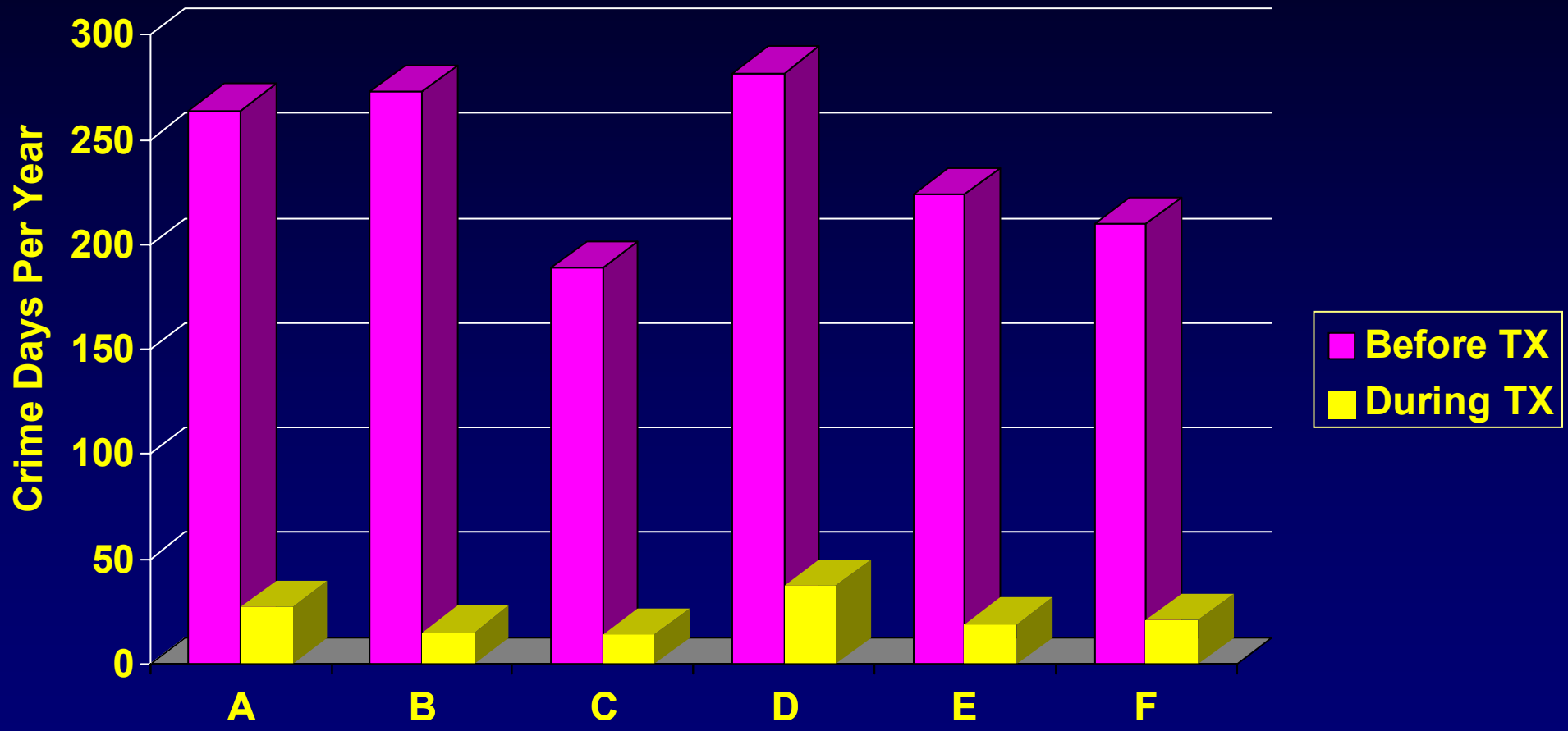
Slide data courtesy of Frank Vocci, MD, NIDA - Reference: Grondblah, L. et al. ACTA PSCHIATR SCAND, P. 223-227, 1990

Impact of MMT on IV Drug Use for 388 Male MMT Patients in 6 Programs



Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

Crime among 491 patients before and during MMT at 6 programs



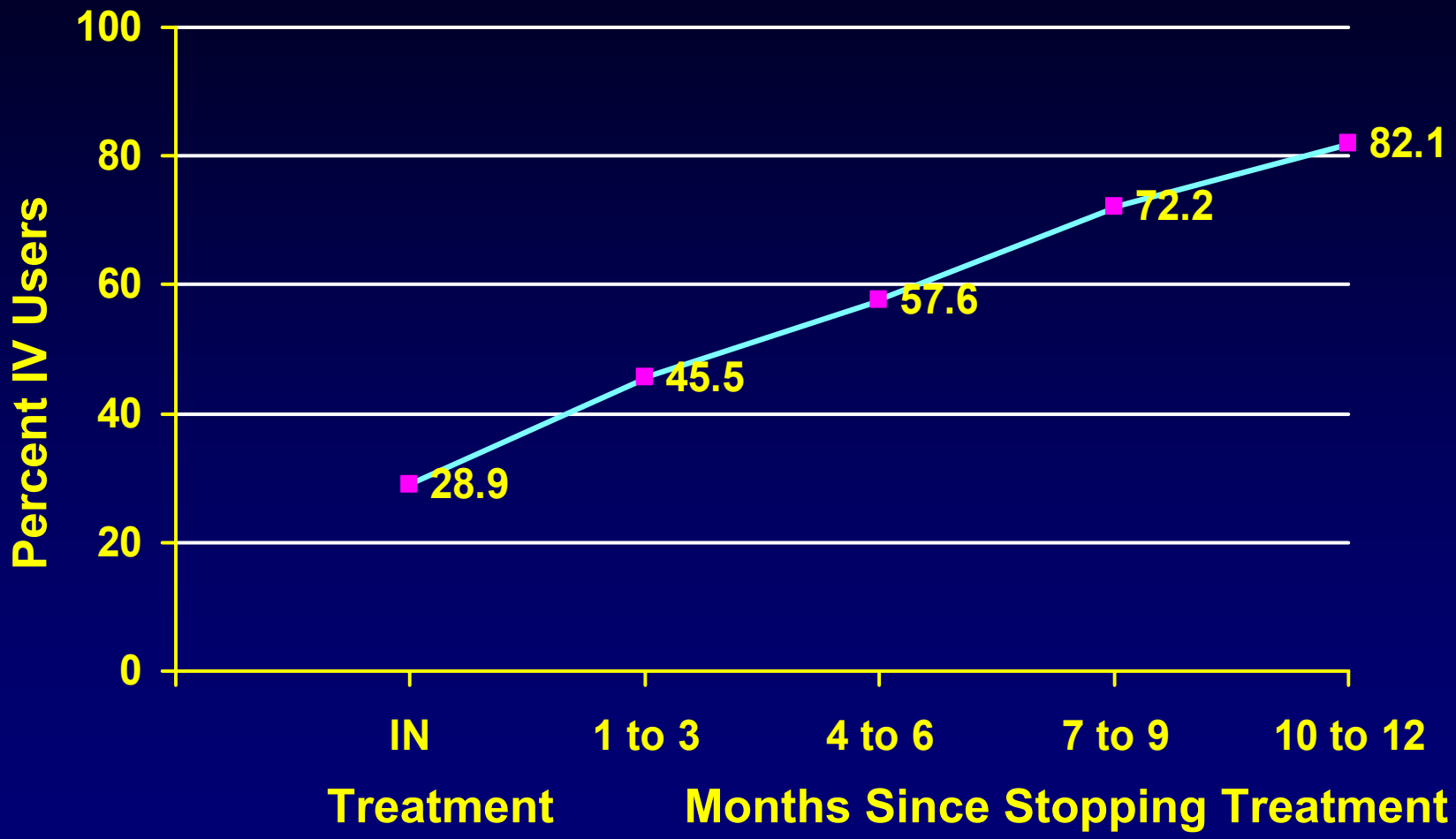
Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

HIV Seropositivity Among Drug Addicts in Bergamo, Italy

Groups	Proportion Positive
Methadone maintenance outpatients	21/74 (28.4%)
Therapeutic Community residents	12/28 (42.9%)
Held in custody	27/66 (40.9%)
Not in treatment	25/51 (52.9%)

Source: Bourne, AIDS and Drug Use: An International Perspective, 1988

Relapse to IV drug use after MMT
105 male patients who left treatment



Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

Other Benefits of Pharmacotherapy for Opioid Addiction

- Increased Employment
- Improved Physical & Mental Health
- Improved Social Function

Intake & Assessment: Minimum Essentials

- Eligibility/Suitability for Treatment
  - Onset Opioid Use/Addiction
  - Recent Use, Number of months use / 12 mo.
  - Current use & pattern at time of admission
    - Days of use /30 days
    - Pattern: Route, Frequency, Amount ($)
  - Observe and Record Objective Signs of Current Physical (opioid) Dependence (CPD)
    - Suggest at least 2 objective signs
  - Consider *Instant* Opiate Drug Screen

Issues in Maintenance:

HOW MUCH?

&

HOW LONG?

How Long Does OAT Last?

Long Enough!!

. . . As long as patient desires and benefits from continued treatment

Statement of Recognition & Gratitude:

Mary Jeanne Kreek, MD

Who as mentor and friend, gave me a foundation in science and guidance in developing clinical guidelines and techniques for safe and effective methadone dosing

SAFE INDUCTION TECHNIQUES

J. Thomas Payte

Orlando, Florida, USA

Patients are 6.7 times more likely to die during induction than untreated heroin addicts (Caplehorn & Drummer, 1999).

42% of drug-related deaths occurred during the first week of OMT (Zador & Sunjic, 2000).

10 OMT deaths are reported — All 10 had been in treatment less than 7 days (Drummer, Opeskin, Syrjanen & Cordner, 1992).

Initial Dose

Degree of Tolerance	Dose Range
Non-Tolerant	10 mg +/- 5
Unknown Tolerance	20 mg +/- 5
Known Tolerance	20-40 mg

Early Induction

Early dose adjustments to reach the “Therapeutic Window” as determined by established opioid tolerance.

-- ***The “Comfort Zone”*** –

Increase dose daily until pt. comfortable during methadone peak levels (3-8 hours after dose) then;

Hold dose for 3-5 days to reach steady-state before further dose adjustments.

REMEMBER STEADY-STATE PHARMACOLOGY!

Early Induction- 2

- Effect of *a* dose IS NOT determined by clinical presentation at 24 hours.

- Initial doses WILL NOT “hold” for 24 hours

- Effect of a given dose is based on status at 3-6 hrs.

  The patient doing well at 3-6 hours does not need a dose increase, even if showing signs/symptoms of withdrawal at 24 hours.

  If patient thinks an increase is needed, repeat dose from previous day and ask patient to return in 3-4 hours for further assessment.

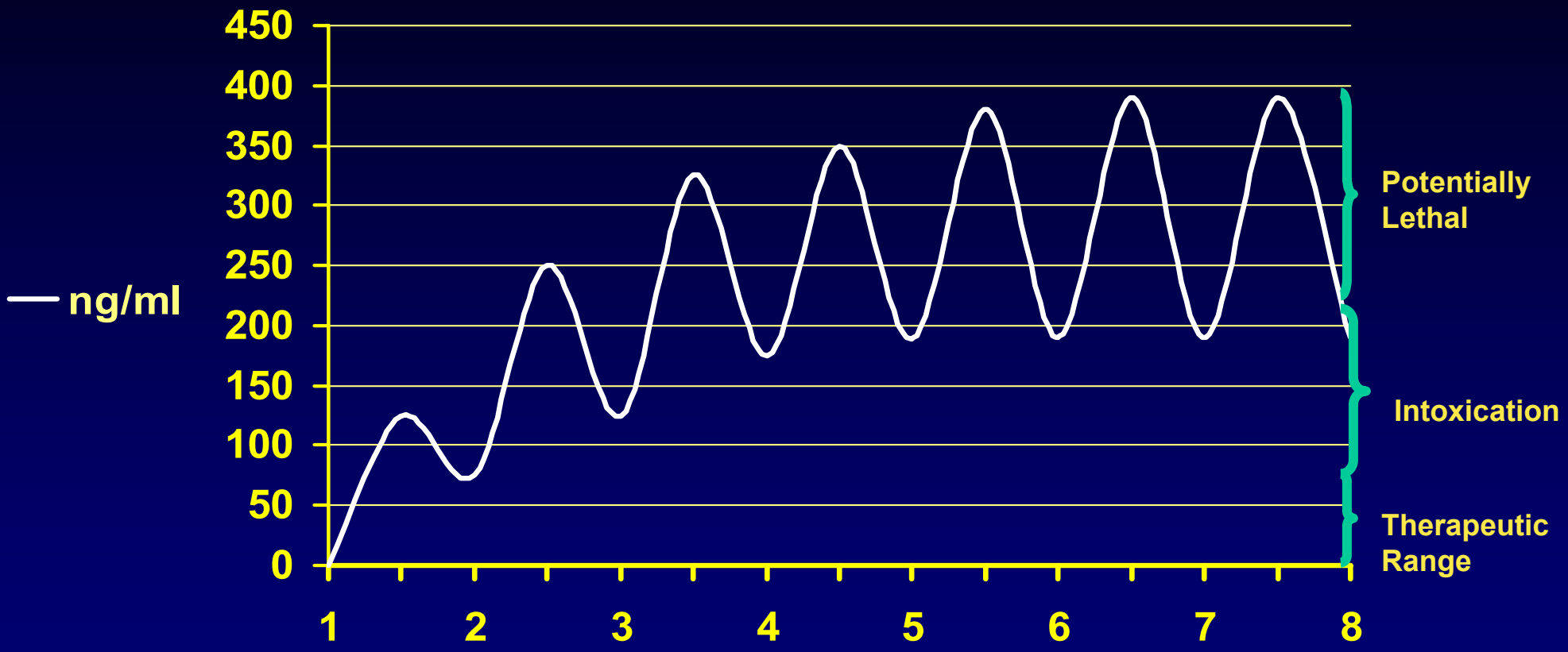
Early Induction- 3

- ANY SIGN OR SYMPTOM OF OVER-MEDICATION DURING EARLY INDUCTION REQUIRES A DOSE REDUCTION!

Beware the subtle signs/symptoms of overmedication; feeling good, extra energy, staying awake to work, etc.

Patients may need more time, not more medication!

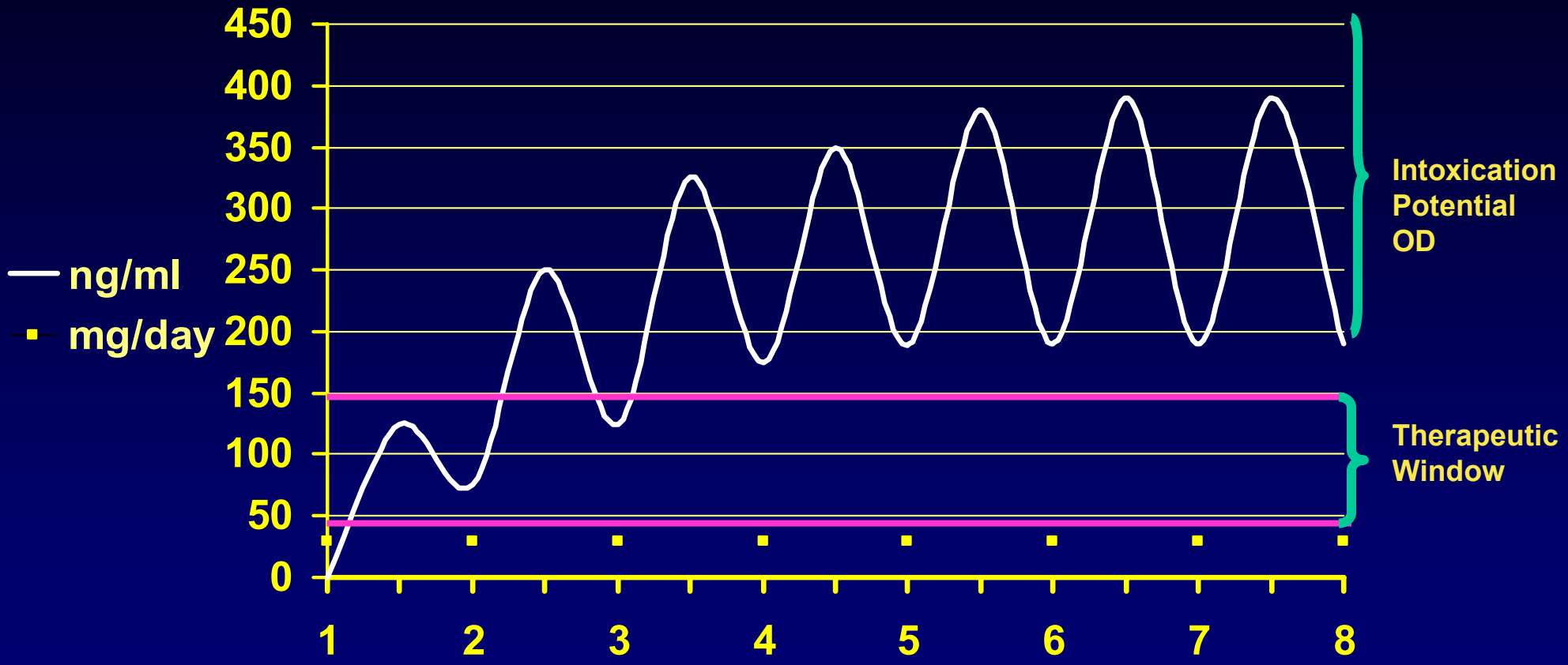
Induction Simulation – Absent to Minimal Tolerance



Dose constant at 30 mg to steady- state.

Note: Peak levels increase daily for 5-6 days with NO increase in dose!

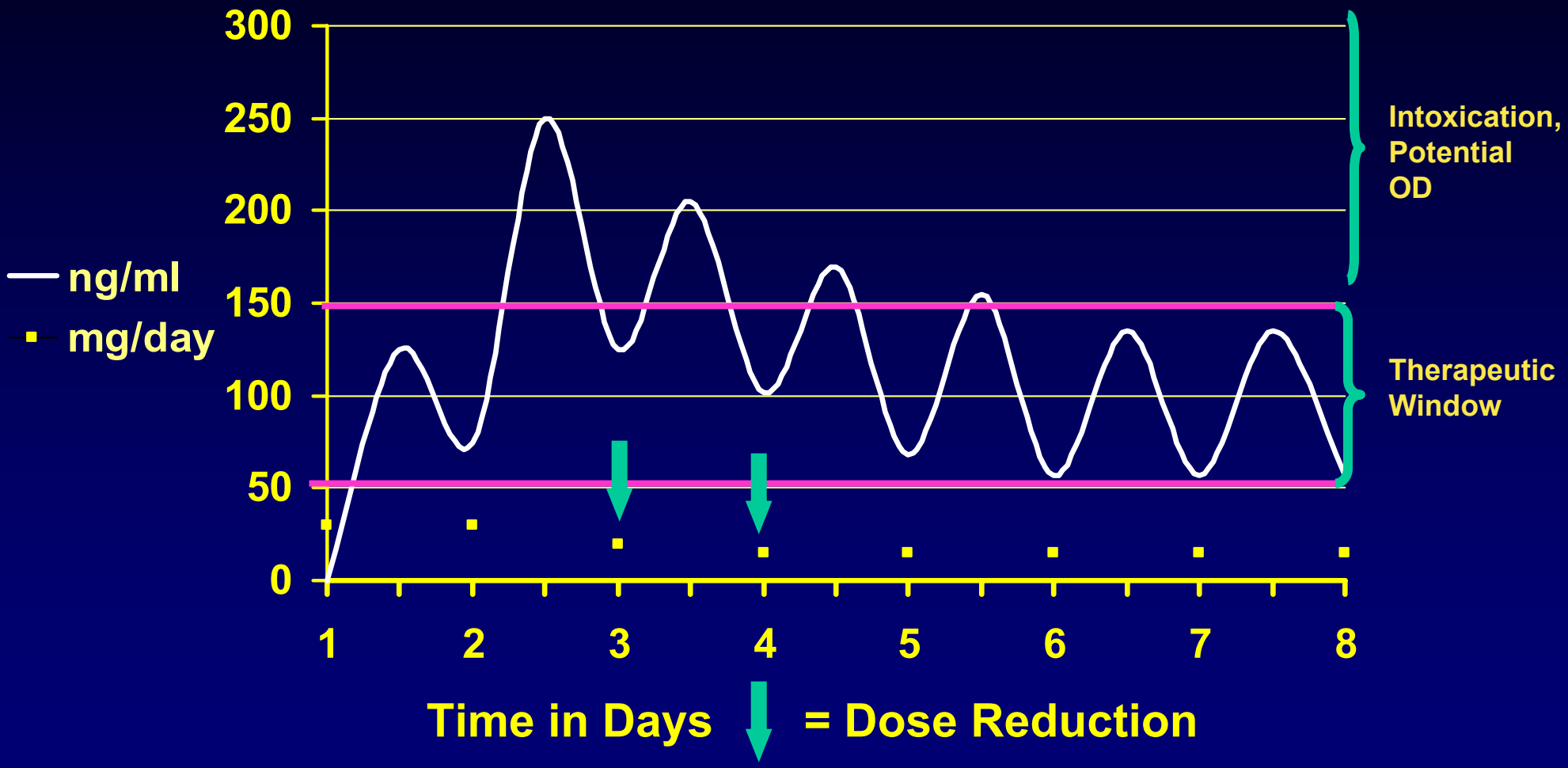
Induction Simulation – Low Opioid Tolerance with failure to reduce dose on day 2 or 3



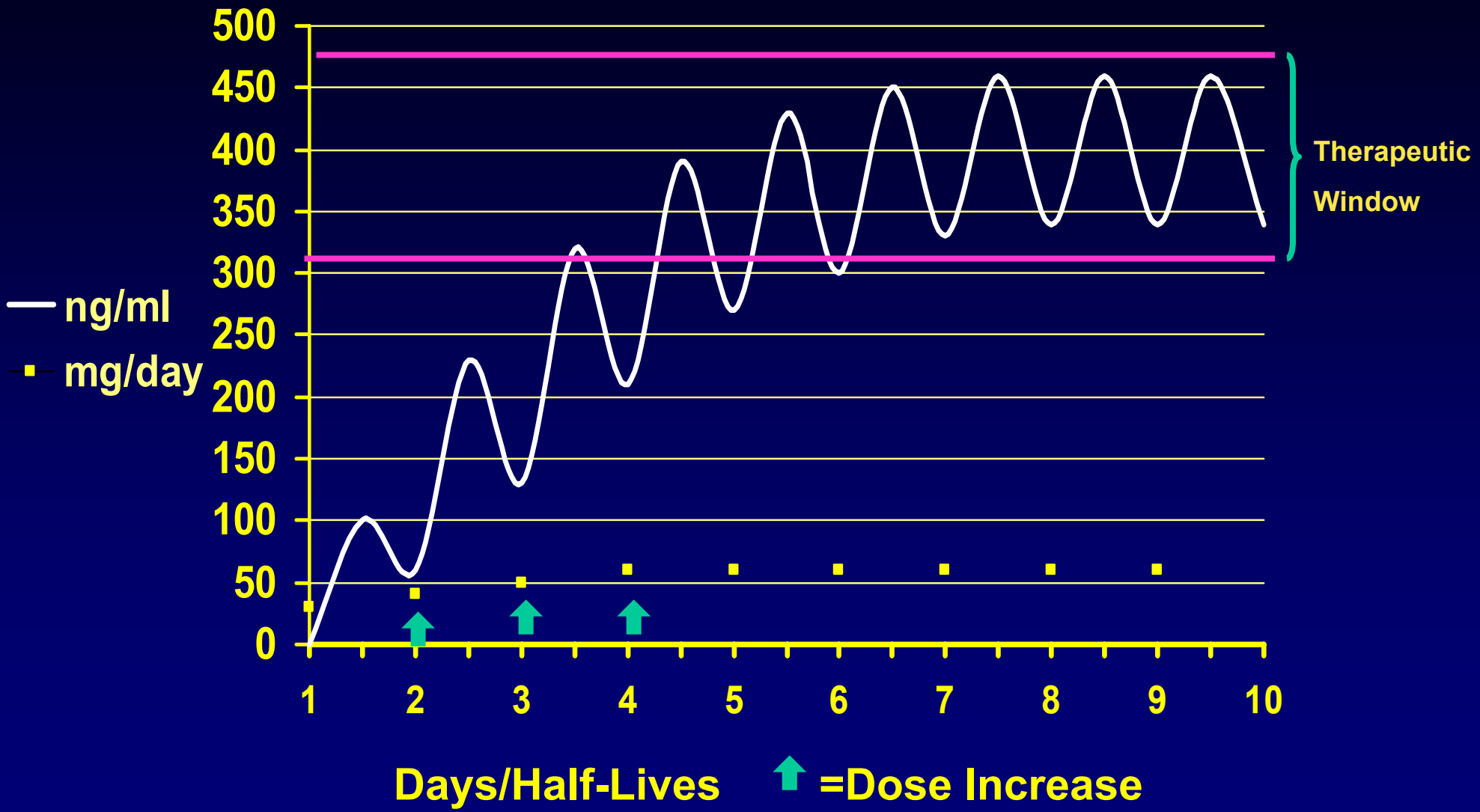
Time in Days

Dose remains constant to steady-state in toxic range

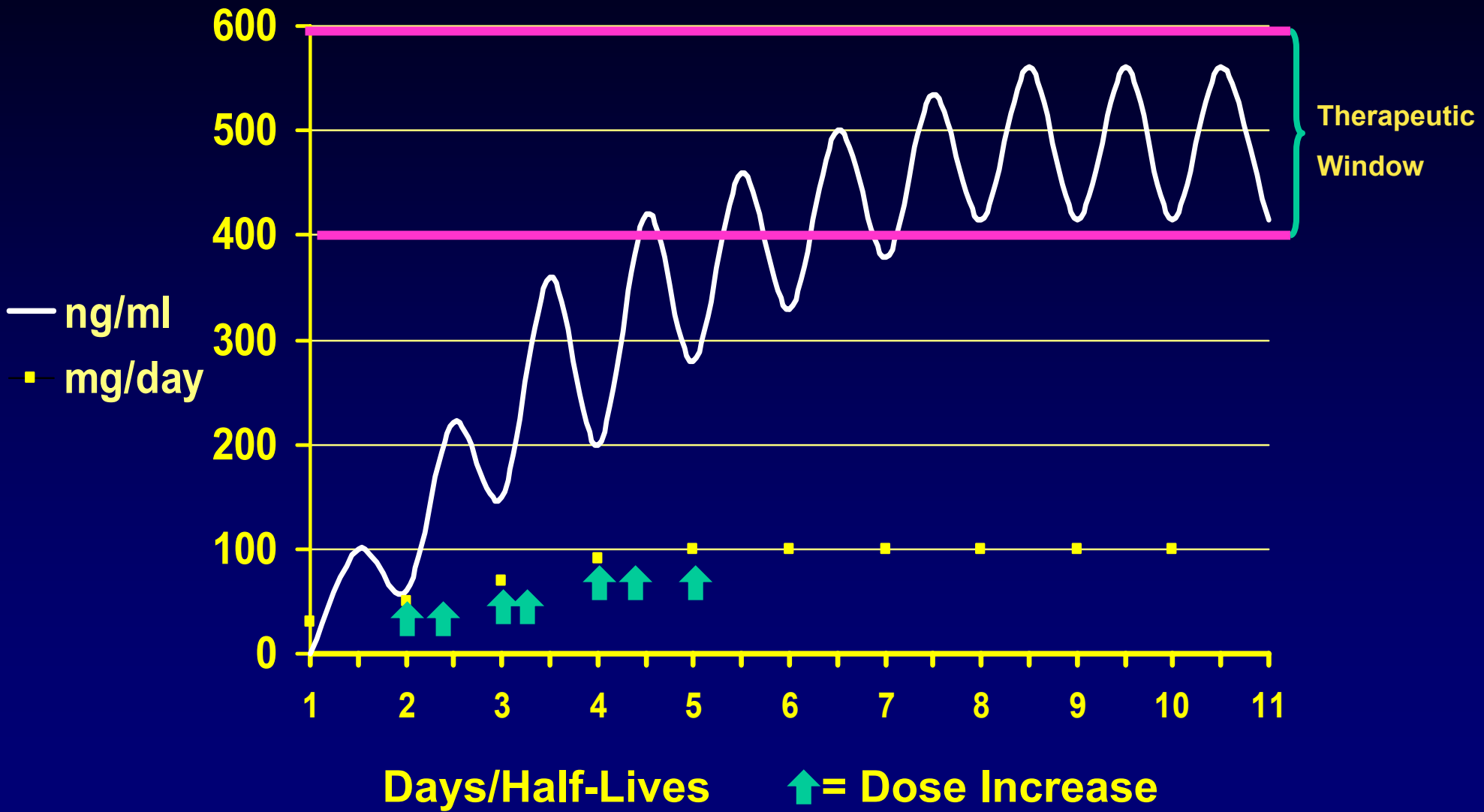
Induction Simulation – Low Dose/Low Tolerance with reduced dose on day 3 & 4



Induction Simulation – Low to Moderate Tolerance



Induction Simulation – Moderate to High Tolerance



Clinical Pearls

Very severe withdrawal signs/symptoms does not mean very high tolerance or the need for higher doses of methadone.

Consider use of instant opiate screens on admission with 2000 ng cut-off

Document signs/symptoms of withdrawal with at least 2 objective signs.

Document daily assessment during induction including basis for decisions to increase dose.

MAINTENANCE:

PRINCIPLES OF ADEQUATE DOSING

OPTIMAL RESPONSE FROM OPIOID AGONIST IN MAINTENANCE TREATMENT

- Prevention of onset of withdrawal syndrome for 24 hours or more
- Reduction or elimination of drug hunger or craving
- "Blockade" of euphoric effects of illicit self-administered opioids

Kreek, 1987 – title change by Payte, 2001

ADEQUACY OF DOSE IS BASED ON 2 FACTORS:

- The amount of medication (size of dose)

  And

- Frequency of dosing; the inter-dose interval (24,12, 8, hrs., etc.)


LOW DOSE


HIGH DOSE

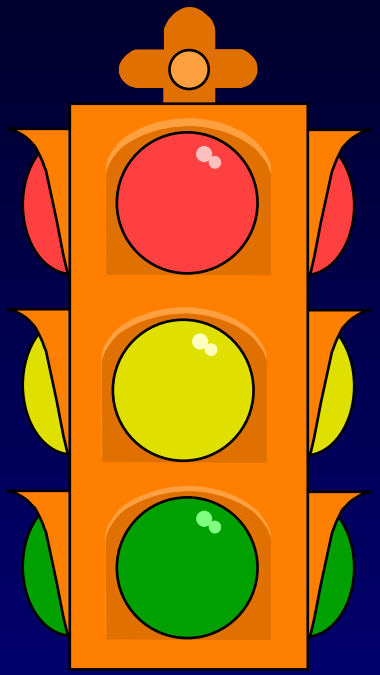
INDIVIDUALIZED !

ADEQUATE DOSE

… based on clinical response

How Much?

ENOUGH!!!



How much is enough?

The amount required to produce the ***optimal response*** for the appropriate duration of time, with an allowance for a margin of effectiveness and safety.

How much is too much?

More than the amount required to produce the ***optimal response,*** or a response that cannot be sustained without escalation of dose due to the continued development of tolerance; ("abnormal normality").

Optimal Vs. Desired Response

The clinician and the patient must speak the same language to ensure realistic expectations and goals of OAT. A pattern of dose escalation in pursuit of the elusive state of “abnormal normality” must be recognized by the patient and the clinician.

The Impossible Dream

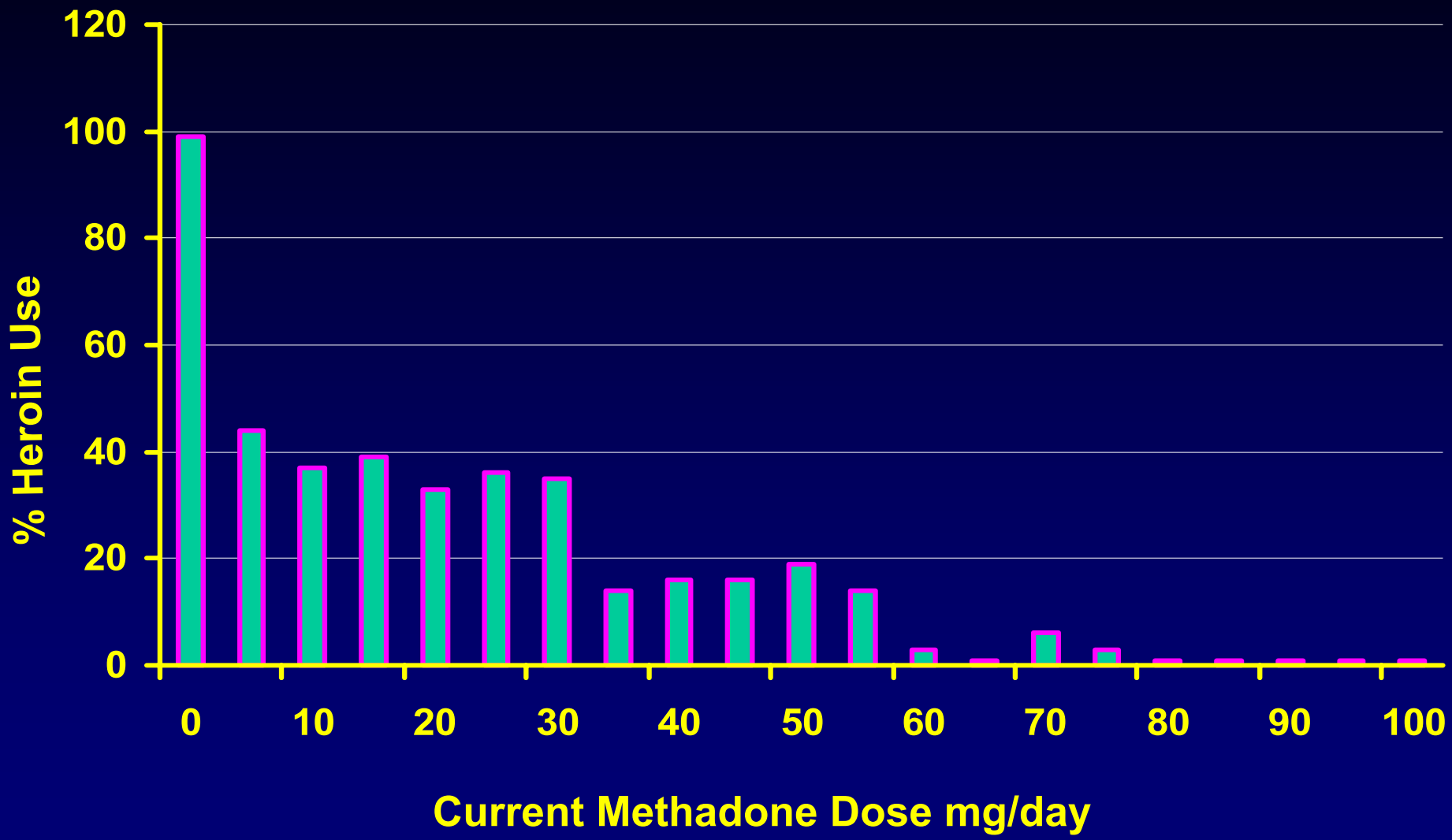
…endless loop:

1. “My dose only holds me a few hours”
2. Increase dose
3. “The increase helped a lot for a few weeks but now it is not holding me – I need an increase.”
4. Goto step 2.

Maximum Dose?

Arbitrary dose ceilings have no foundation in science or clinical medicine. Programs with "dose caps" can expect problems with accreditation. Dose caps are not supported by CSAT, AMTA, ASAM or any credible entity.

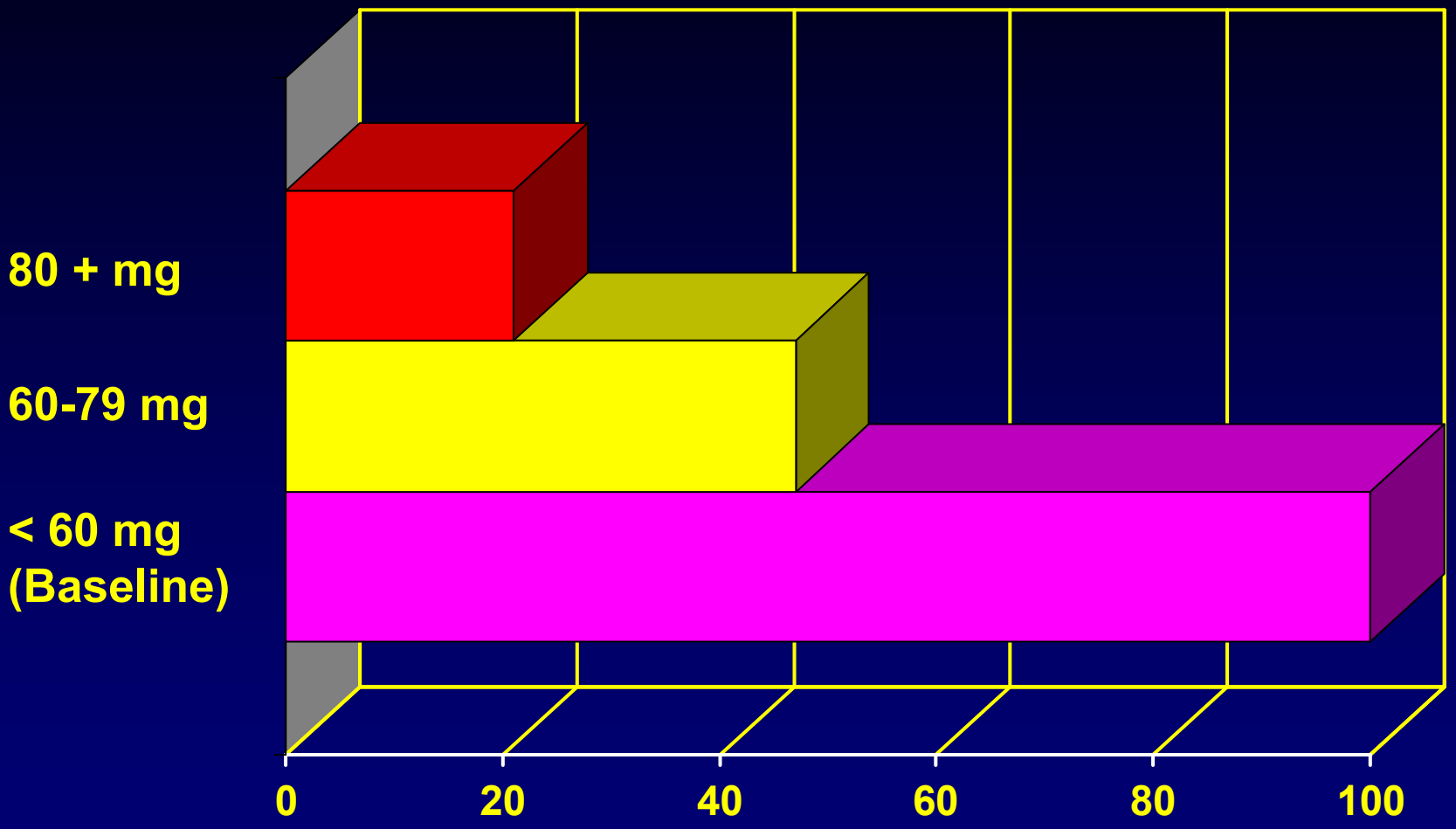
Recent Heroin Use by Current Methadone Dose



J. C. Ball, November 18, 1988

Retention in Treatment Relative to Dose

Relative Risk of Leaving Treatment



Adapted from Caplehorn & Bell - The Medical Journal of Australia

MEDICALLY SUPERVISED WITHDRAWAL

MEDICALLY SUPERVISED WITHDRAWAL FOR THE HIGHLY MOTIVATED PATIENT WHO HAS:

- No alcohol/drug use/abuse (>6mo.?)
- Stable living/social/employment situation
- No illegal activities, warrants, or cases pending
- Relative psychiatric/medical stability
- Friends and associates from outside drug culture
- Non-drug related hobbies, interests, and pursuits
- Support system and continuing care in place

MEDICALLY SUPERVISED WITHDRAWAL TECHNIQUES:

- Graded reduction or taper (usually outpatient)
- Accelerated withdrawal, clonidine assisted with early antagonist induction (in or outpatient)
- Rapid or Ultra-rapid antagonist induced withdrawal under anesthesia or sedation (preferable inpatient – not widely accepted)
- Crossover to Buprenorphine* from low to moderate dose methadone or LAAM, then taper from Bup

  * - coming to a theater near you, soon!

Variable Term Methadone Taper

- Dose cuts proportional to recent dose level– up to 10% (100 to 90, 50 to 45, 30 to 27, etc.)
- Variable hold at each level, usually 5-10 days, faster or slower as tolerated.
- Patient options (safety net):
  - To hold dose as needed
  - To return to a higher dose if needed
  - To resume dose cuts when stable

METHADONE BLOOD LEVELS

why? When? Where?

Literature Highlights

Loimer 11/92:

HPLC to Abbott TDxFPI coefficient of correlation 0.96
Optimum results BPL > 200 ng/ml at all times

Loimer 8/92:

Optimal BPL > 150 ng/ml
Best results in patients receiving > 90 mg/day
Therapeutic drug monitoring (BPLs) give optimum results

Dole 11/88:

150-600 ng/ml at all times for stability

Postulates derangement endogenous ligand-narcotic system.
Defect compensated by methadone...
MM is corrective, not curative

2- Literature Highlights

Tennant, Rawson, Cohen, Tarver, & Clabouth 3/84:

Patients on 80 mg/day methadone

Good performers -- 24 hr. BPL 410 ng/ml

Poor performers -- 24 hr. BPL 101 ng/ml

Holmstrand, Anggard & Gunne 2/78:

Best results steady-state levels > 200 ng/ml

Lower levels -- illicit drug use and poor psych/social

Walton, Thornton & Wahl 7/78:

Suggest serial methadone levels finding dramatic clinical improvement and flattening of the curve with split dose in MM patients experiencing difficulty on single dose

3- Literature Highlights

The Relationship Between Mood State and Plasma Methadone Concentration in Maintenance Patients

The

Dyer KR, White JM, Foster DJR, Bochner F, Menelaou A, Somogyi AA. Royal Adelaide Hospital, Adelaide, Australia

Journal of Clinical Psychopharmacology,
2001 Vol 21(1):78-84.

This study demonstrates that significant mood changes occur in response to changes in methadone concentration, and these are more pronounced in "non-holders" (early onset withdrawal) than "holders" (stable for 24 hours).

Dyer & Associates Continued

The difference in w/d severity between self-reported holders and non-holders was not related to either methadone dose or trough plasma methadone concentration, demographic or other individual characteristics but, rather;

to the significantly more rapid rate of decline in plasma concentration during the period from the peak concentration until the trough.

…high peak/trough ratio

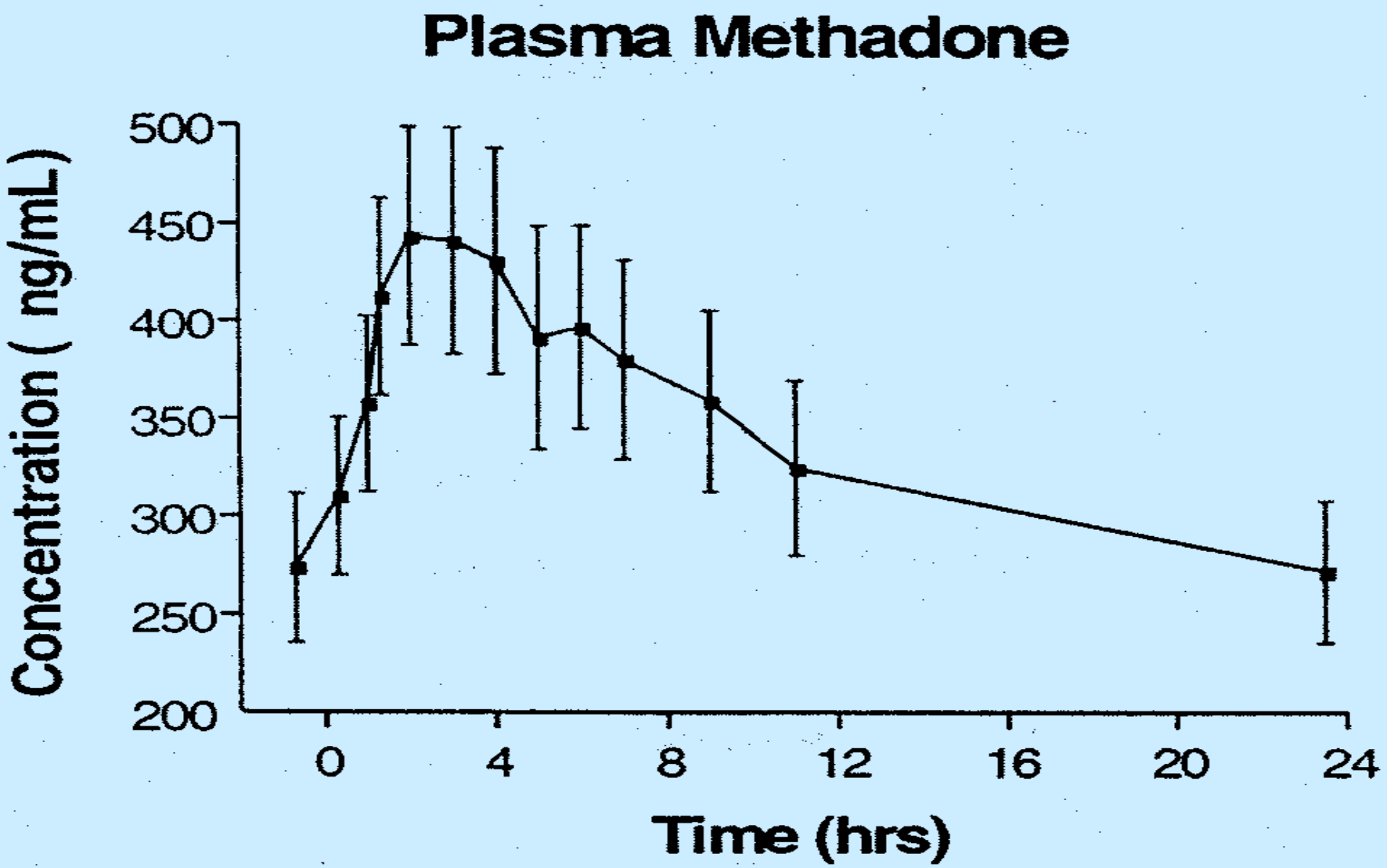
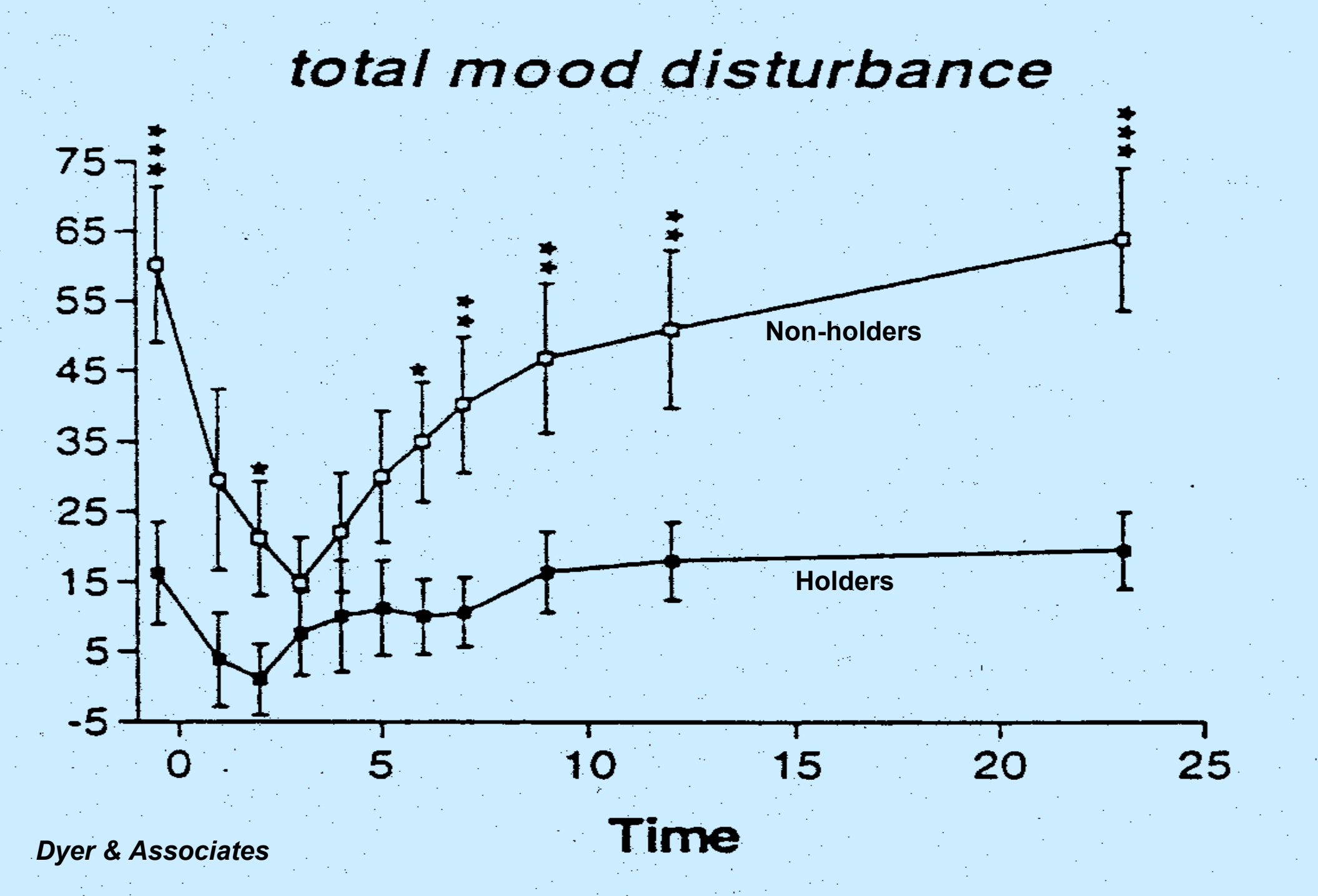


FIG. 1. Mean (± SEM) plasma methadone concentration-time profile during a single 24-hour interdosing interval in 18 methadone patients.


total mood disturbance
75
65
55
45
35
25
15
5
-5
0
5
10
15
20
25
Time
Non-holders
Holders
Dyer & Associates

Serum Methadone Levels

- Define Peak to Trough ratio, the rate of decline or metabolism
- Define the optimum dosing interval to maximize benefits of OMT
- Clinical Picture / Dose Incongruities
- Suspected Drug Interactions
- Justification of “unusual” dose levels/schedules
- Monitor effectiveness of divided dose schedules

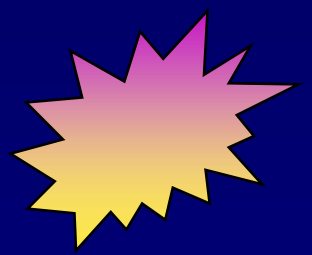
Interpretation of Serum Methadone Levels

Peak or trough Levels alone are of negligible clinical utility in determining adequacy of a given dose.

Dose adequacy is determined clinically!

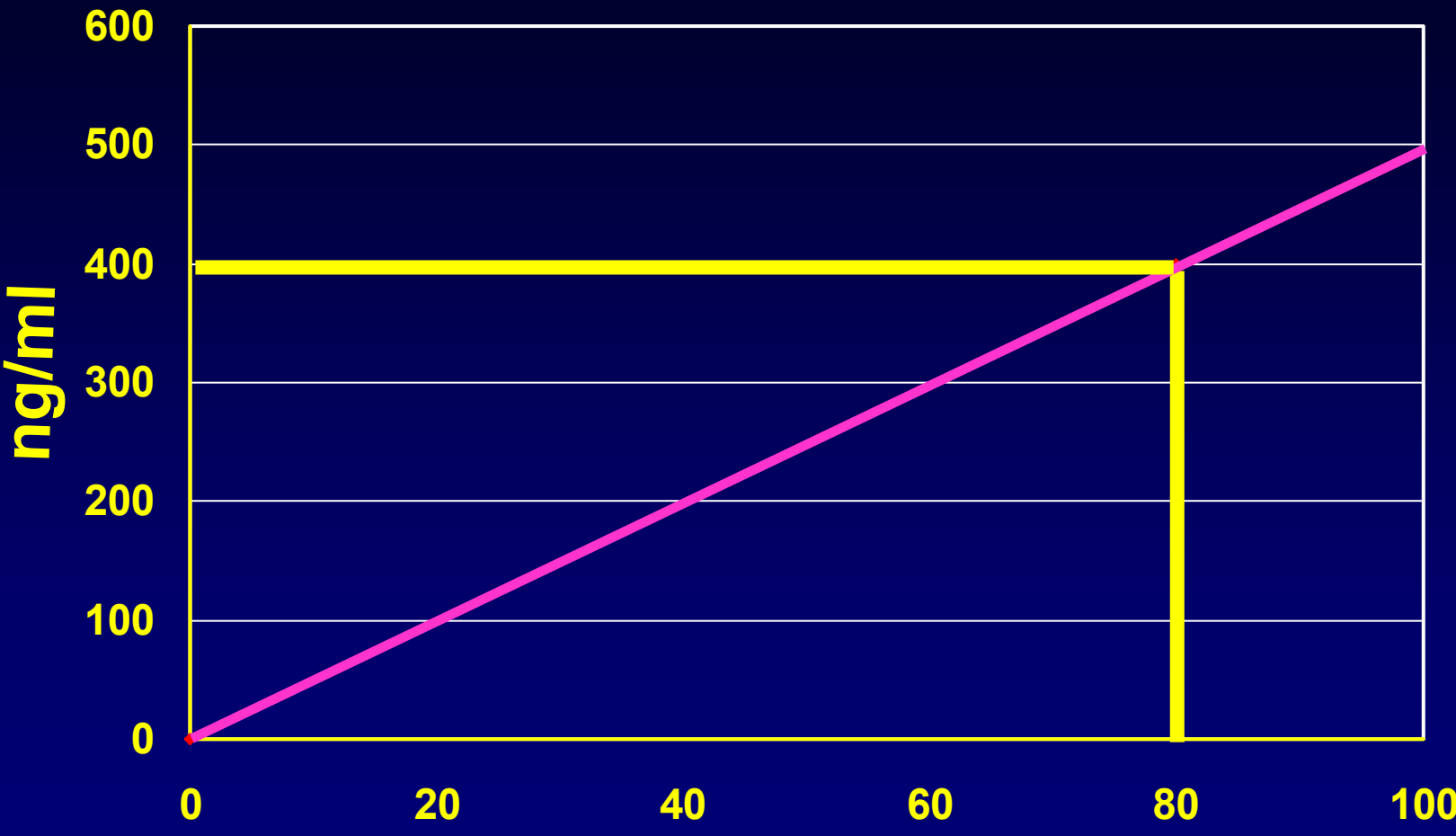
Optimum levels for cross-tolerance ("Blockade") are thought to be 400 ng/ml or more

Peak/Trough Ratio ideally less than 2, 700/400=1.75, values > 2 suggest rapid metabolism, 800/200=4



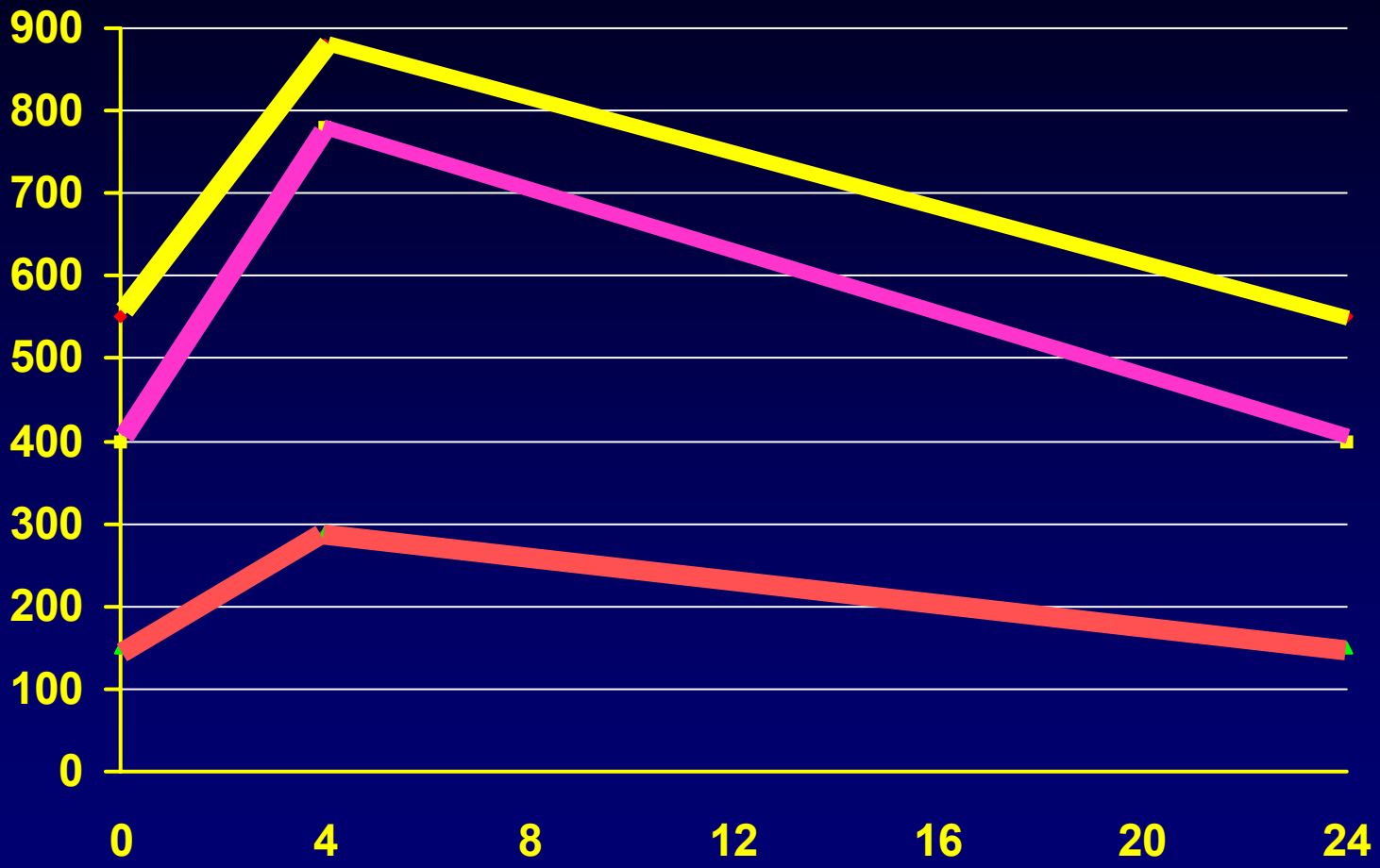
Rate of change !

There is linear relationship between dose and methadone levels but NOT to clinical response



Payte & Khuri - Adapted from Wolff et al 1991

Early 4 and 24 Hour Methadone Levels



Early Levels
p/t = 1.6

"Ideal" Levels?
p/t = 1.9

Minimal Levels
p/t = 1.9

Payte & Khuri - Early Levels : Inturissi & Verebely 1972, Kreek 1973

In-House Methadone Levels

- Semi-quantitative urine/serum methadone
- Fluorescence Polarization Immunoassay (FPI) Abbott TDx
  - 0.96 coefficient of correlation with HPLC (Loimer, 1992)
- Abbott Adx (FPI)
  - Useful and practical for office-based clinical application

My dose isn't "holding" me

- Environment?
- Stressors?
- Alcohol?
- Other drugs/medications?
- Vitamins? (especially C)
- Urinary pH?
- Clinically adjust methadone dose
- Methadone blood levels?

Payte - Khuri

“Not Holding” Strategies

- Cognitive, Behavioral Interventions
- Increased contact, counseling, therapy
- Alter urinary pH?
- Is patient fixing? - Raise dose
- Split Dose?

Payte - Khuri

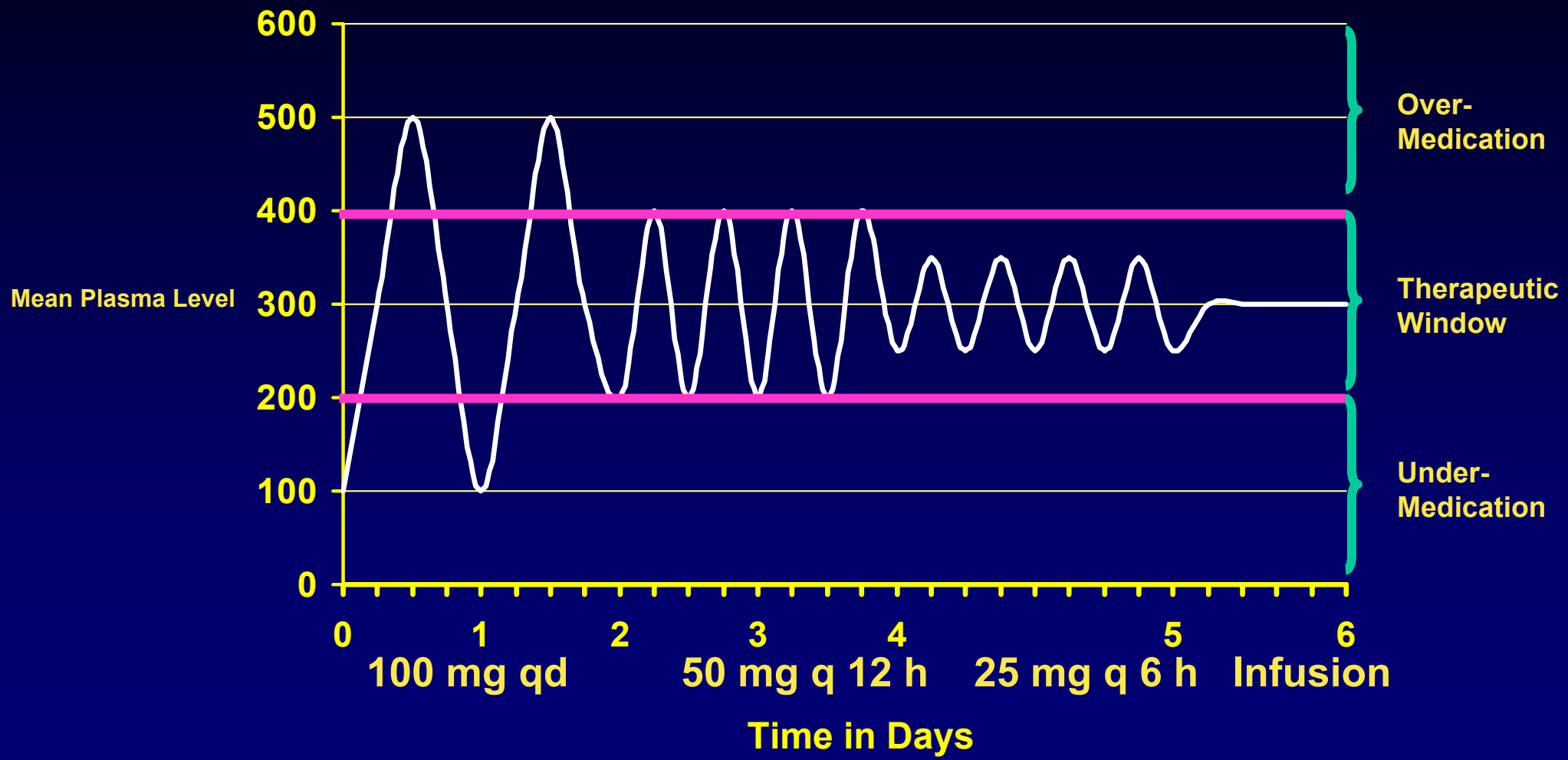
Cytochrome P-450 Enzyme Activity
Drug Interactions - Methadone

- Induction
  - Rifampin
  - Phenytoin
  - Ethyl Alcohol
  - Barbiturates
  - Carbamazepine
  - Nevirapine (Viramune)

Cytochrome P-450 Enzyme Activity
Drug Interactions - Methadone

- Inhibition
  - Fluconazole
  - Cimetidine
  - Erythromycin
  - Fluvoxamine (Luvox)
  - Ketoconazole
  - Nefazodone (Serzone)
  - Ritonavir (Norvir)

Steady-State – Fluctuations Determined by Frequency of Dose



WHO Guide to Good Prescribing: Essentials of Pharmacology in Daily Practice. Annex 1.
http://www.docnet.org.uk/who/ggp/homepage.htm

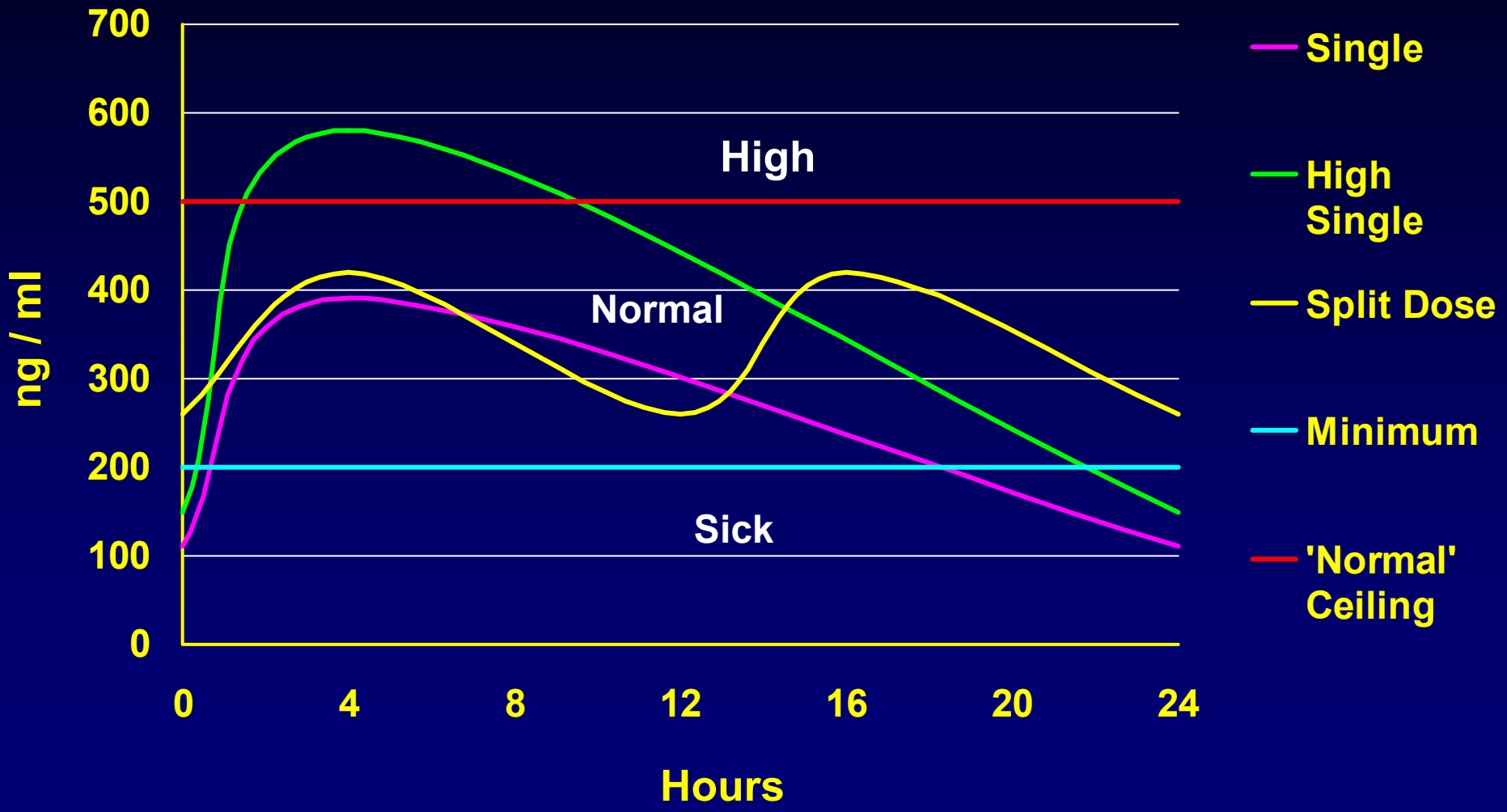
Applications of preceding

Patient c/o waking up sick daily but is sedated 3-6 hrs. after dose:

Dose increase will not make the dose last longer, just increase the fluctuation between over and under medication.

Increase frequency not dose!

Rapid Metabolizer - High Single and Split Dose Simulation



Split Dose Induction

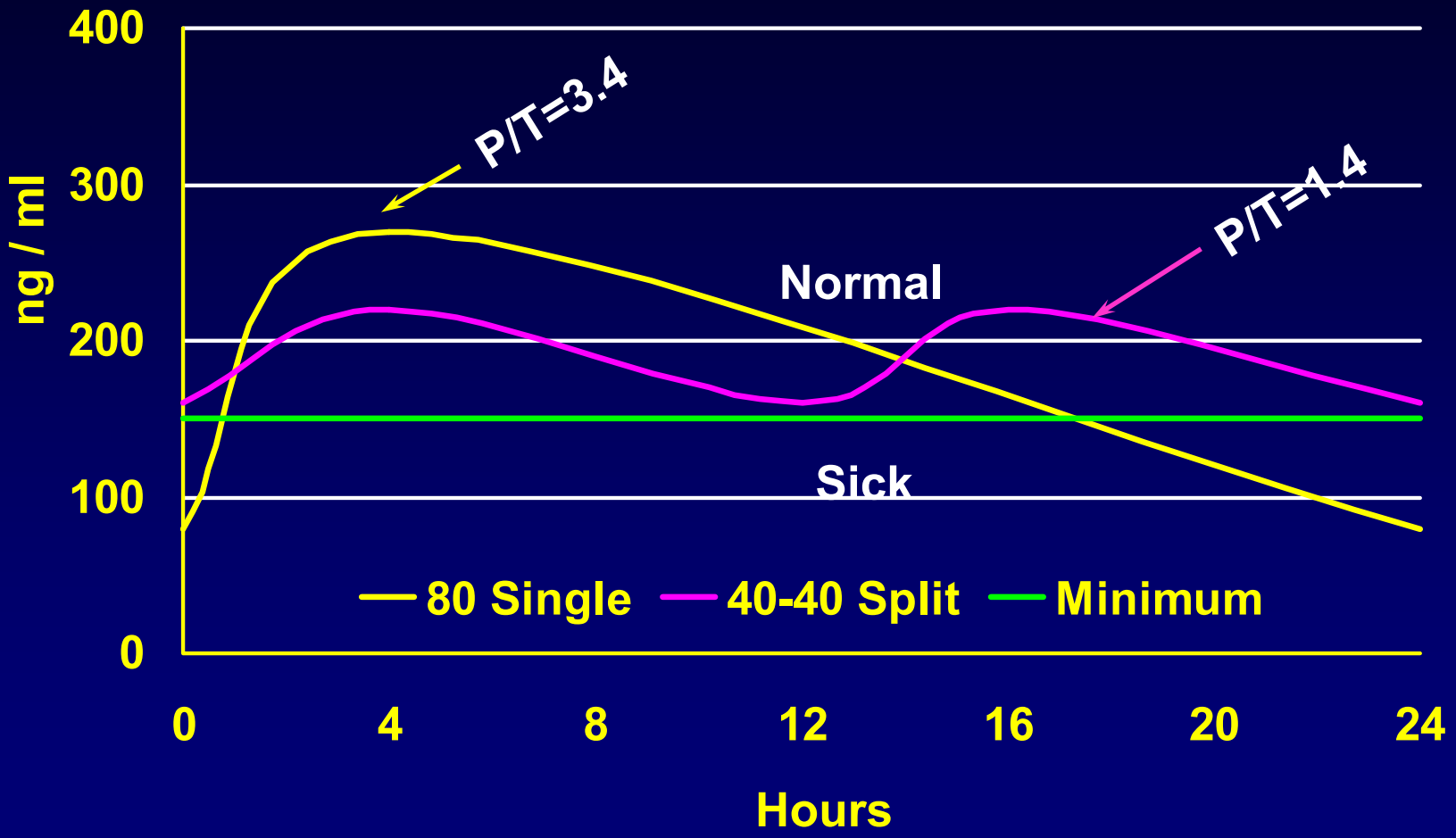
- Day 1: 100% of current dose, observed
  50% of dose to take in 12 hours

- Day 2 and beyond: 50% of dose q 12 h

Note: Poor results from starting with half the usual dose on day 1

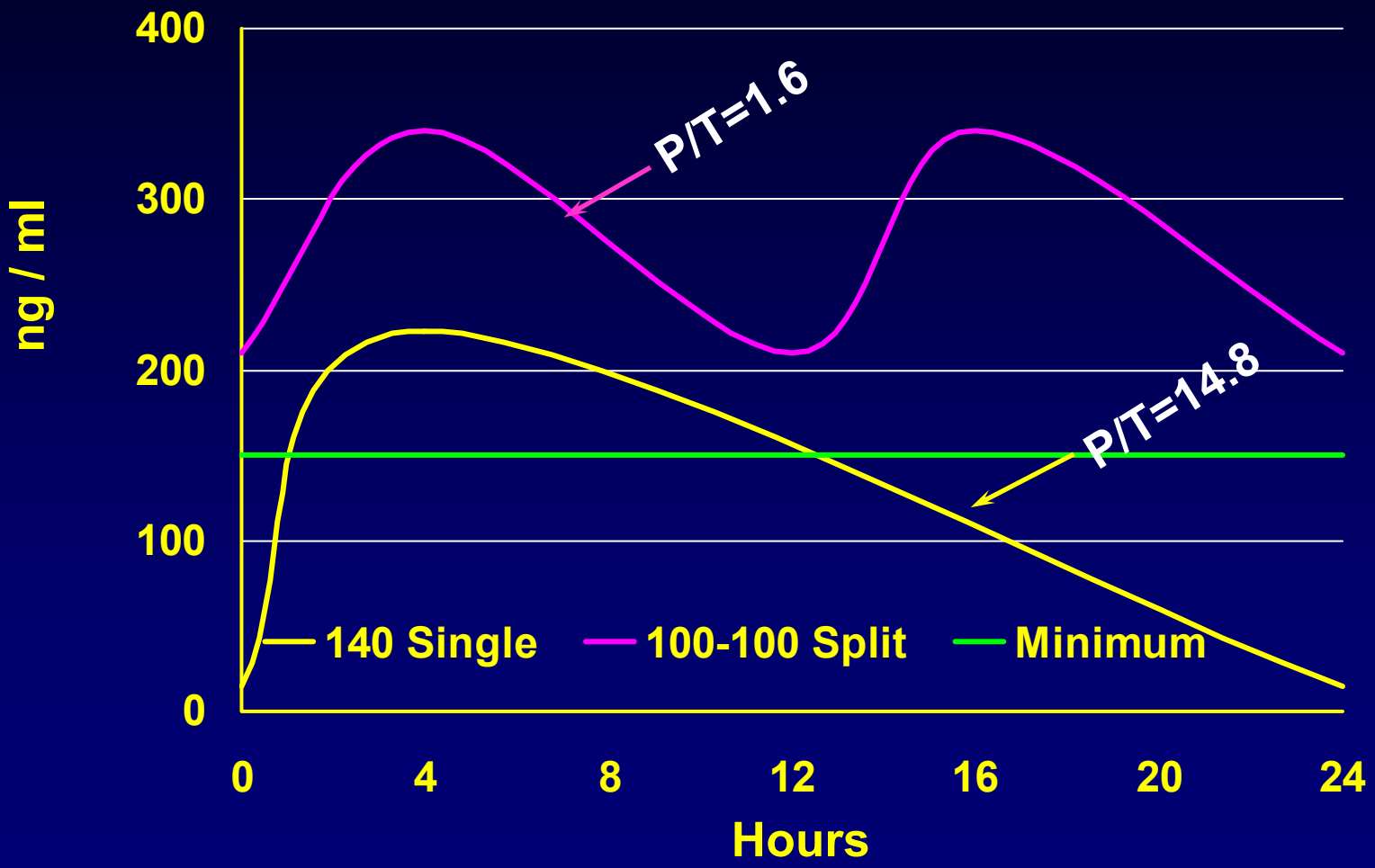
Pregnancy Case Study @ 6 mo.

" I wake up sick & my baby moves a lot!"

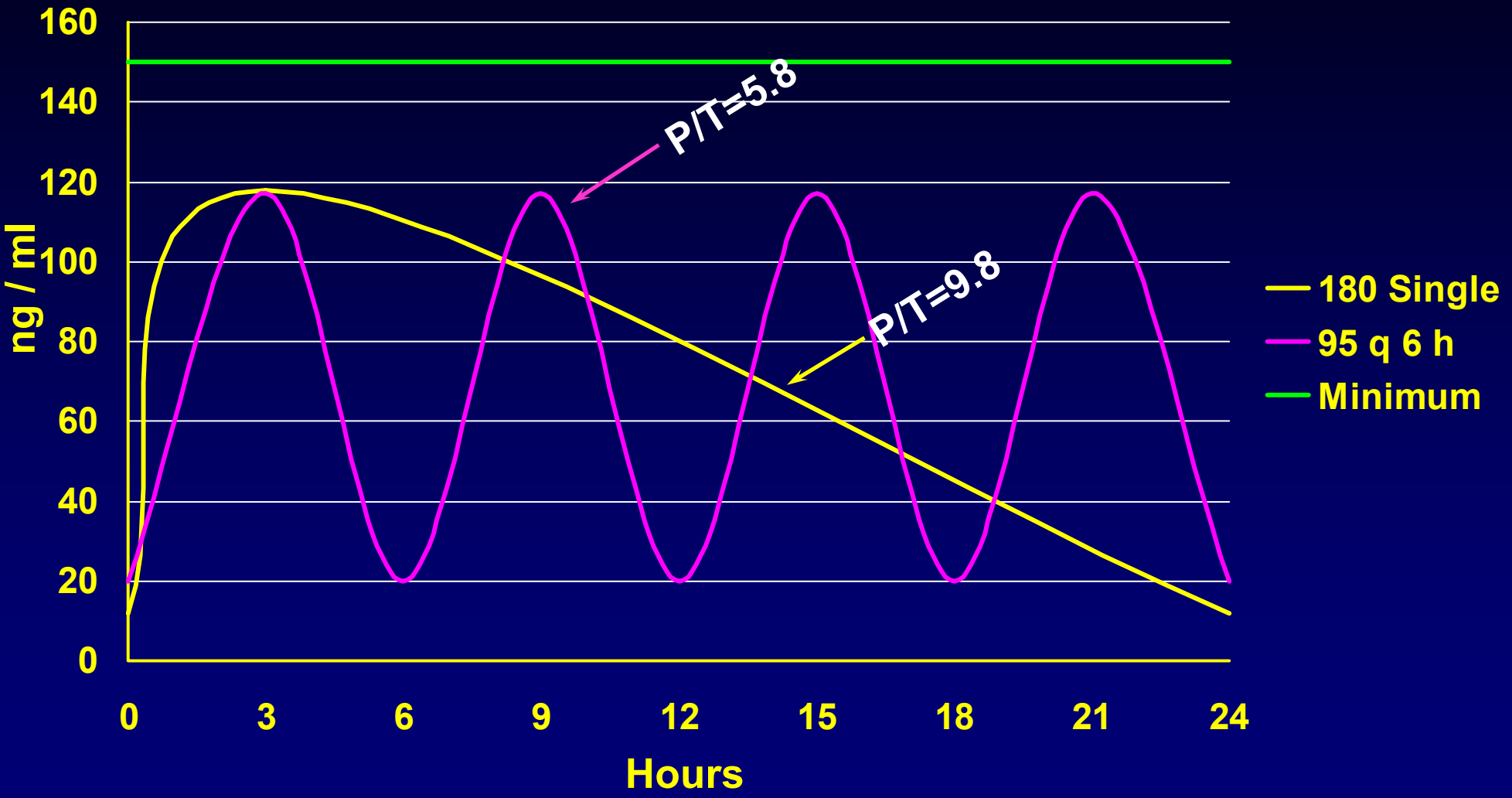


Phenytoin Case Study

"You can't be sick - you are on 100 mg!"

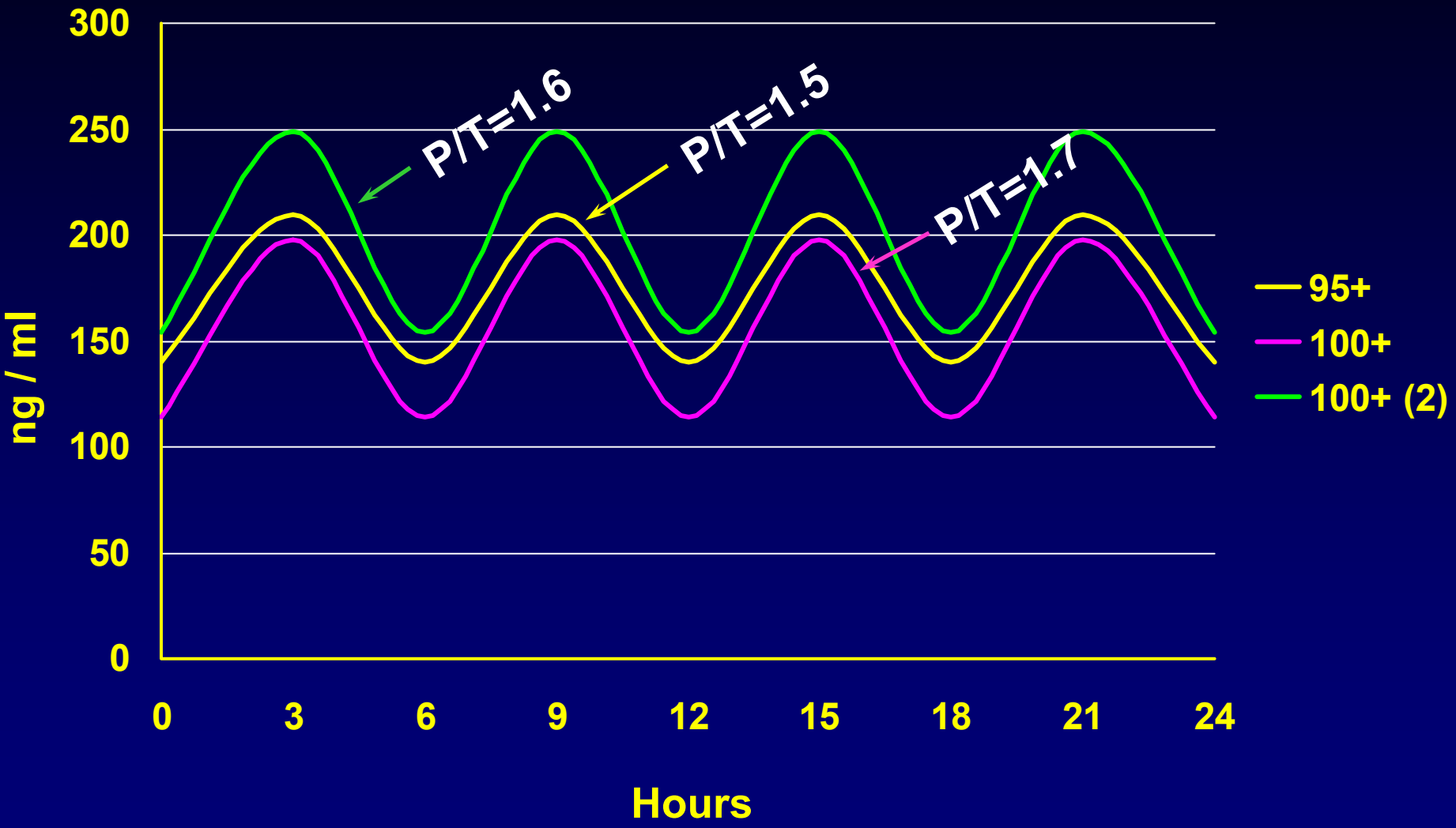


Carbamazepine Case Study



2- Carbamazepine Case Study

Methadone q 6 h + cimetidine



OMT

IN PERINATAL

ADDICTION

Perinatal Addiction - 1

- MMT is but a single element in the variety of services needed for optimal care of the pregnant opioid dependent patient.
- Comprehensive MMT with adequate prenatal care can reduce the incidence of obstetrical and fetal complications, in utero growth retardation, and neonatal morbidity and mortality (Finnegan, 1991)

Perinatal Addiction -2

- Withdrawal? - Rarely appropriate during pregnancy (ASAM 1990)
  - Same recidivism as non-pregnant opioid addicts (Finnegan, 1990)
  - Slow withdrawal between 14 and 32 weeks (Kaltenbach, 1992) [??? Schnoll]
- Dose of methadone should be individually determined and adequate to control craving and prevent withdrawal syndrome

Perinatal Addiction -3

- MMT patients who become pregnant should be continued at established dose. A mid-trimester reduction may be appropriate in anticipation of 3rd trimester dose increase.
- Altered pharmacokinetics during 3rd trimester often require dose increases and often a split dose to “flatten the curve” and improve maternal and fetal stability.

Perinatal Addiction -4

- There is no consistent correlation between maternal methadone dose and the severity of neonatal withdrawal syndrome (Stimmel et al., 1982).
- Protocols are available for scoring signs of opioid withdrawal to guide the appropriate use of medications to facilitate a safe and comfortable withdrawal of the passively addicted neonate (Finnegan, 1985).

Perinatal Addiction -5

- Breast-feeding may be encouraged during MMT - if not otherwise contraindicated (Kaltenbach, 1992).
- Multiple longitudinal studies find that methadone-exposed infants score well within the normal range of development (Kaltenbach, 1992).

Perinatal Addiction -6

- Obstacle and barriers to MMT must be removed for the pregnant patients.
- More research is needed on innovative models of treatment including medically supervised withdrawal during pregnancy with residential care, intensive relapse prevention and monitoring, high-risk prenatal care. When appropriate hospitals, clinics and individual obstetricians could provide methadone maintenance.

Withdrawal during Pregnancy

- The patient refuses to be placed on methadone maintenance.
- The patient lives in an area where methadone maintenance is not available.
- The patient has been stable during treatment & requests withdrawal prior to delivery.
- The patient has been so disruptive to the treatment setting that the treatment of other patients is jeopardized, necessitating the removal of the patient from the program.

Jarvis & Schnoll,1994

PAIN AND OPIOID ADDICTION

Chronic Pain VS Opioid Addiction

- Opioid tolerance & physical dependence **DO NOT** equal Opioid Addiction
- Pain patients without addiction should not be treated in MMTP
- Addiction patients without pain disorder should not be treated in pain clinics
- Chronic pain patients with addictive disease may be treated in both

Opioid Addiction

- Opioid tolerance and physical dependence AND
- Loss of Control Indices:
  - Continued use despite adverse consequences
  - Illicit or inappropriate drug seeking behavior
    - In response to craving or drug hunger
    - In the absence of pain or withdrawal

Pseudo Addiction

- in chronic pain patient

- Inadequate Treatment of Pain
- "Apparent" Drug Seeking Behavior
  - Effort to achieve adequate analgesia
  - Early refill, doctor shopping, etc.
    - Manipulation seen as "addictive behavior"
    - May be seen as non-compliance
- "Cured" by adequate treatment of pain

Chronic Pain Disorder

- Opioid Tolerance
- Opioid Physical Dependence
- Absence of illicit or inappropriate drug seeking behavior
  - No drug hunger in absence of pain
  - No loss of control
- No “doctor shopping”
- Little tendency to escalate dose over time

Pain Management During Maintenance Pharmacotherapy

- Continue maintenance without interruption
- Provide short-acting opioid analgesics as needed
- Higher doses may be required at increased frequency - titrated for relief of pain
- Do not use **Mixed Agonist/Antagonist** or partial or weak agonist drugs
- Monitor prescriptions closely

Program Guidelines for Hospitalized Maintenance Patients

- Discuss methadone treatment before admission
- Have a clear understanding regarding:
  - Uninterrupted maintenance treatment
  - Adequate treatment for pain
    - Note: The recovery room is not the place to negotiate pain management
- Program physician should be available to hospital staff

Hospital Guidelines For Maintenance Patients

On admission the hospital staff should:

- Notify program of admission and confirm time and amount of last dose
- Ensure continuity of maintenance pharmacotherapy
- Treat patients with compassion, dignity and respect
- Notify program *before* discharge to ensure continuity of care

NPO For Methadone Maintained Patients

- 24 hours after last oral dose of methadone:
  - IM methadone, 40-50% of oral dose every 12 hours OR
  - IM morphine sulfate 20-25% of oral methadone dose every 6 hours
- Monitor for over/under medicating
- Methadone for continued maintenance or substituted morphine, *will not provide analgesia!!*